NOVEL (HOMO-)NAZAROV APPROACHES TO COMPLEX POLYCYCLES AND APPLICATION TO BIOACTIVE TARGETS

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NOVEL (HOMO-)NAZAROV APPROACHES TO COMPLEX POLYCYCLES AND APPLICATION TO BIOACTIVE TARGETS

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This thesis is dedicated to my family: my wife Jenny, father Timmy and mother Annette, sister Cortny, grandmother Mary Ann and late grandfather Jack, and my spiritual family (especially those at Embry Hills and West Philly). These are the folks who helped me realize my intellect and always believed in me, even when I did not believe in myself. These are the people who made me who I am, and the people I hope will influence others through my work for years to come.

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A long time ago, in small town called Russellville, Alabama, a little shop stood on the main highway running through the town where people would hock their goods for a little temporary cash. Now, not many people would expect an interest in science to begin in a place such as a pawn shop, but that is where my story begins. My grandfather, Jack Williams, owned that shop. One day, someone brought in a small, simple microscope set with a number of slides of different plants and insects and pawned it to my granddad, and never came back to pick up their merchandise. After 60 days, that microscope set became property of Jack's Pawn Shop, and my granddad gave that set to me. Thus begins the story of how a small town kid from "nowhere" Alabama became interested in science.

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LIST OF SYMBOLS AND ABBREVIATIONS

A	Acceptor
Å	Angstrom
ABL	α-Alkylidene-γ-butyrolactone
AcOH	Acetic Acid
Ac_2O	Acetic Anhydride
AgO_2CF_3	Silver (I) trifluoroacetate
AgOTf	Silver (I) trifluoromethanesulfonate
$AgSbF_6$	Silver (I) antimony hexafluoride
$AlCl_3$	Aluminum trichloride
$Al(OTf)_3$	Aluminum (III) trifluoromethanesulfonate
AMS	α-Methylstyrene
ANFC	Aza-Nazarov-like Friedel-Crafts-type
API	Active pharmaceutical ingredient
Ar	Aryl or Argon
ATR	Attenuated total reflection
$Au(PPh_3)Cl$	Gold (I) triphenylphosphine chloride
$BF_3•Et_2O$	Boron trifluoride diethyl etherate
$Bi(OTf)_3$	Bismuth (III) trifluoromethanesulfonate
Br or Br^-	Bromo- or Bromide
Br_2	Bromine
br	Broad
brsm	Based on recovered starting material
C	Carbon or Celsius
^{13}C	Carbon-13
CAN	Cerium (IV) ammonium nitrate
$Ca(NTf_2)_2$	Calcium (II) bis(trifluoromethanesulfonimide)
CCl_4	Carbon tetrachloride
$CDCl_3$	Chloroform-*d*
$CeCl_3$	Cerium (III) chloride
$CeCl_3•7H_2O$	Cerium (III) chloride heptahydrate
CF_3	Trifluoromethyl
CH_2Cl_2	Dichloromethane
Cl or Cl^-	Chloro- or Chloride
cm	Centimeters
cm^{-1}	Inverse centimeters or Wavenumbers
CO	Carbon monoxide or Carbonyl
CO_2	Carbon dioxide
$(COCl)_2$	Oxalyl chloride

Conc.	Concentration
COSY	Correlation spectroscopy
Cp_2TiCl_2	Titanocene dichloride
CrO_3•3,5-DMP	Chromium (III) oxide-3,5-dimethylpyrazole
Cu	Copper
$Cu(ClO_4)_2$	Copper (II) perchlorate
$Cu(OTf)_2$	Copper (II) trifluoromethanesulfonate
D	Donor or Deuterium
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DACP	Donor-acceptor cyclopropane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DHF	Dihydrofuran
DIBAL-H	Diisobutylaluminum hydride
dil.	Dilute
DIPEA	Hunig's base or Diisopropylethylamine
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
dr	Diastereomeric ratio
DS	Dean-Stark
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron ionization
eq. or equiv.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
EtOAc	Ethyl acetate
F or F^-	Fluoro- or Fluoride
^{19}F	Fluorine-19
FC	Friedel-Crafts or Friedel-Crafts-type
$Fe_2(CO)_9$	Diironnonacarbonyl
FHN	Formal homo-Nazarov
FTIR	Fourier transform infrared spectroscopy
g	Gram
$Ga(OTf)_3$	Gallium (III) trifluoromethanesulfonate
Grubbs II	Grubbs's 2nd generation catalyst

H or H_2	Hydrogen
^1H or H^+	Proton
HCl	Hydrochloric acid
(Het)Ar	(Hetero)aryl
HF	Hydrofluoric acid
$HgSO_4$	Mercury (II) sulfate
H_2O	Water
H_2SO_4	Sulfuric acid
HMBC	Heteronuclear multiple bond correlation
$HNTf_2$	Bis(trifluoromethanesulfonimide) or Triflimide
HOMO	Highest occupied molecular orbital
hr	Hour
HRMS	High resolution mass spectrometry
11β-HSD1	11β-hydroxysteroid dehydrogenase 1
HSQC	Heteronuclear single quantum correlation
hv	Light
Hz	Hertz
I or I^-	Iodide
I_2	Iodine
IBX	2-iodoxybenzoic acid
Im	Imidazole
$InCl_3$	Indium (III) chloride
$In(OTf)_3$	Indium (III) trifluoromethanesulfonate
i-Pr	Isopropyl
i-PrBr	Isopropyl bromide
IPrAuCl	1,3-Bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold (I) chloride
IR	Infrared spectroscopy
J	Coupling constant
kcal	Kilocalories
K_2CO_3	Potassium carbonate
KI	Potassium iodide
$La(OTf)_3$	Lanthanum (III) trifluoromethanesulfonate
LDA	Lithium diisopropylamide
LHMDS or LiHMDS	Lithium bis(trimethylsilyl)amide
$LiAlH_4$	Lithium aluminum hydride
LiCl	Lithium chloride
$LiEt_3BH$	Lithium triethylborohydride (Superhydride)
LUMO	Lowest unoccupied molecular orbital
M	Brönsted/Lewis acid or Molar
m	Medium or Multiplet

[M]	Metal complex
Me	Methyl
MeCN	Acetonitrile
MeI	Iodomethane
MeOAc	Methyl acetate
MeOH	Methanol
MeOTf	Methyl trifluoromethanesulfonate
mg	Milligram
$Mg(O\textit{t}\text{-Bu})_2$	Magnesium *tert*-butoxide
$Mg(OTf)_2$	Magnesium trifluoromethanesulfonate
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
min	Minutes
mL	Milliliter
mmol	Millimole
MO	Molecular orbital
mol	Mole
MS	Mass spectrometry or Molecular sieves
m/z	Mass per unit charge
N or N_2	Nitrogen (elemental)
$NaBH_4$	Sodium borohydride
NaCl	Sodium chloride
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NaHMDS	Sodium bis(trimethylsilyl)amide
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
Na_2SO_2Ph	Sodium benzenesulfinate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyllithium
$n\text{-}Bu_4NPF_6$	Tetrabutylammonium hexafluorophosphate
NEt_3	Triethylamine
NHC	*N*-Heterocyclic carbene
NH_4Cl	Ammonium chloride
$Ni(OTf)_2$	Nickel (II) trifluoromethanesulfonate
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Np	Naphthyl

Nuc	Nucleophile
O or O_2	Oxygen
OEt	Ethoxy
OH	Hydroxyl
OMe	Methoxy
OTf	Triflate or Trifluoromethanesulfonate
PCC	Pyridinium chlorochromate
PEG-400	Polyethylene glycol-400
PFK	Perfluorokerosene
Ph	Phenyl
PhH	Benzene
PMP	*para*-Methoxyphenyl
$PO(OEt)_2$	Diethylphosphonate
ppm	Parts per million
prep-TLC	Preparative thin layer chromatography
pyr	Pyridine
q	Quartet
RCM	Ring-closing metathesis
R_f	Retention or retardation factor
Rh	Rhodium
$Rh_2(esp)_2$	Bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid]
$Rh_2(oct)_4$	Rhodium octanoate dimer
$Rh(PPh_3)_3Cl$	Rhodium (I) tris(triphenylphosphine) chloride or Wilkinson's catalyst
rt	Room temperature
s	Strong or Singlet
sat. aq.	Saturated aqueous
$Sc(OTf)_3$	Scandium (III) trifluoromethanesulfonate
sept	Septet
SmI_2	Samarium iodide
$SnCl_4$	Tin (IV) chloride
$Sn(OTf)_2$	Tin (II) trifluoromethanesulfonate
SO_2Ph	Phenyl sulfonyl
t	Triplet
TBDPS	*tert*-Butyldiphenylsilyl
TBS or TBDMS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Trifluoromethanesulfonic acid

THF	Tetrahydrofuran
$TiCl_4$	Titanium (IV) chloride
$TiCl_4$•2THF	Titanium (IV) chloride tetrahydrofuran complex
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl or 4-Methylphenylsulfonyl
TsN_3	Tosyl azide
TsOH	Tosic acid
tt	Triplet of triplets
w	Weak
$Yb(OTf)_3$	Ytterbium (III) trifluoromethanesulfonate
Zn	Zinc
$Zn(OTf)_2$	Zinc (II) trifluoromethanesulfonate
°	Degrees
α	Alpha
β	Beta
γ	Gamma
δ or Δ	Delta
π	Pi
σ	Sigma
µg	Microgram
µL	Microliter
µm	Micron

SUMMARY

Complex carbocycles and heterocycles make up a large majority of natural product scaffolds and active pharmaceutical ingredient cores. As a result of this, developing methods to obtain such scaffolds in new, greener, and more modular ways remains an invaluable objective within the synthetic organic community. In this thesis, a number of exciting new methodologies have been developed to access some of these scaffolds, and significant progress is shown toward the application of these methodologies to access pharmaceutically-relevant cores: (1) a chemodivergent and catalytic interrupted, formal homo-Nazarov cyclization to access densely functionalized carbocycles, (2) the application of homo-Nazarov methodology toward the anticancer natural product, Propolisbenzofuran B, and (3) the application of Nazarov-like, Friedel-Crafts methodology toward the antimalarial natural product, Flinderole A. These methodological transformations are tolerant of a variety of functionalities, thus giving broad substrate scope. These syntheses seek to have modular key transformations that will allow formation of a wide variety of non-natural analogs, thus providing rapid access to a compound library useful in the study of structure-activity relationships.

CHAPTER 1. INTRODUCTION

1.1 Synthetic Organic Chemistry and Its Utility

Organic chemistry continues to be one of the most important physical sciences to study, having significant impact in pharmaceuticals, agriculture, materials science, and other industries. Perhaps one of the most important reasons to study organic chemistry is its relevance in the understanding of biological systems. Quite simply, biological systems are nothing more than a series of self-assembling, self-replicating, organic reactions. When considered in this manner, understanding how to develop new small molecule active pharmaceutical ingredients (APIs) and drug delivery systems becomes considerably more simplified. Small molecule APIs are seen as simply "hands" that fit within protein or enzyme "gloves" to either activate or shut down biological processes. Physical properties of APIs are distilled down to finding an intricate balance of solubility in aqueous solutions and their "greasiness," or low-polarity, in order to pass through cell membranes. When the desired physical properties of a drug compound are known and a lead is established, work can then focus on other issues, such as metabolic stability, toxicology, and formulations development.

Oftentimes, biological systems produce a number of secondary molecules to their normal metabolic processes (called secondary metabolites) with interesting bioactivities ranging from antibacterial, anticancer, and anti-inflammatory to anti-parasitic and antiviral activities. These secondary metabolites, also known as natural products, are often the basis of new APIs. These natural products often have immaculately complex molecular scaffolds, from macrocyclic to polycyclic scaffolds, multiple stereocenters, and

a number of different functional groups. One major drawback of these natural products molecules is that they are often extracted in sub-milligram amounts from multiple kilograms of raw material. As a result of this, manufacturing new APIs by this extraction method is impractical.

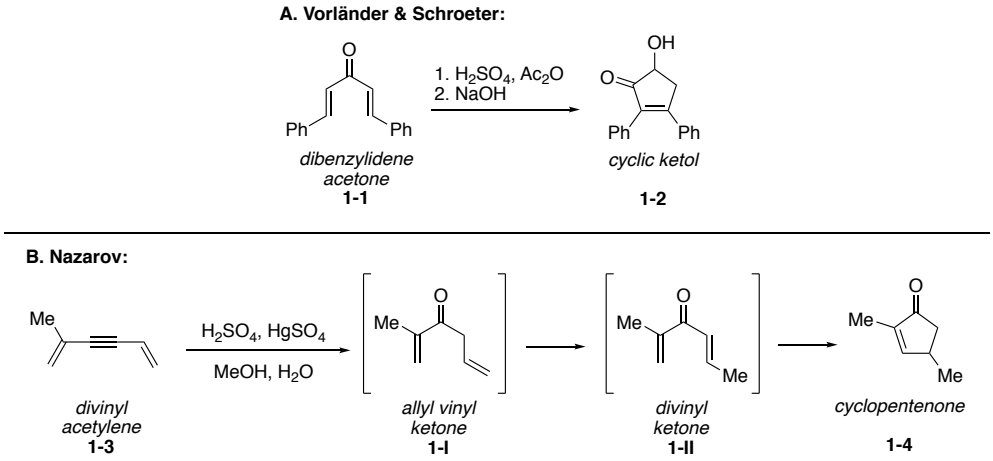
Because of the impracticality of producing new APIs from natural products by extraction, it is often tasked to the organic chemist to develop a synthetic route toward such molecules. Much more importantly, the organic chemist needs to have a large, and ever expanding, "toolbox" full of organic reactions to tackle these daunting molecules. Therefore, developing methodologies as new "tools" to take on these complex molecular scaffolds remains a constant focus of the synthetic organic community. As new therapeutics become generally more complex, they often become increasingly more expensive to manufacture. This leads to the first emphasis of new methodological developments – enhanced efficiency. Secondly, as of the 1990s, stricter regulations were placed upon drug manufacturers regarding the development of chiral drugs.[1] Because of this, many drug developers have focused on progressing single enantiomers as drug candidates instead of racemic mixtures. As such, a need had arisen for more stereoselective methodologies to ease issues within the synthesis and development of chiral drug compounds. Lastly, APIs are often complex, densely functionalized molecules that present a number of significant synthetic hurdles.[2] With this in mind, significant focus should be placed on the development of versatile, modular methodologies with very broad substrate scope.

With the growing need for more synthetic "tools" in the organic chemist's toolbox, especially those for constructing 5- and 6-membered (hetero)cyclic compounds,

two powerful methodologies remain underexplored in the literature: aza-Nazarov and homo-Nazarov reactions (for the construction of 5- and 6-membered (hetero)cycles). Nazarov cyclization methodologies have been extensively explored and well represented in the synthesis of bioactive molecules. However, the aza-variant of the Nazarov (for the construction of 5-membered nitrogen heterocycles) still remains underexplored and underutilized in the syntheses of natural products. Homo-Nazarov reactions, on the other hand, are still relatively recent synthetic methods. As such, there remains much room for exploration of new chemical space, the development of synthetic routes utilizing homo-Nazarov transformations toward natural products and their core scaffolds. This thesis will focus on the recent advancements in these methodologies and their utilization in the synthesis of bioactive natural products.

1.2 Nazarov Cyclization Reactions[3]

Although unknown to its authors at the time, the Nazarov cyclization reaction was first discovered in 1903 by D. Vorländer and G. Schroeter after exposing dibenzylidene acetone to concentrated sulfuric acid and acetic anhydride, and then hydrolyzing with sodium hydroxide to give a cyclic ketols (Scheme 1.1A).[4] In 1941, the Russian chemist Ivan Nazarov began investigating the rearrangement of allyl vinyl ketones, and found that exposing divinyl acetylenes to an acid promoter led to hydrolysis, forming allyl vinyl ketones, followed by isomerization of the allyl group to give a divinyl ketone, which then undergoes cyclization to form cyclopentenone products (Scheme 1.1B).[5]

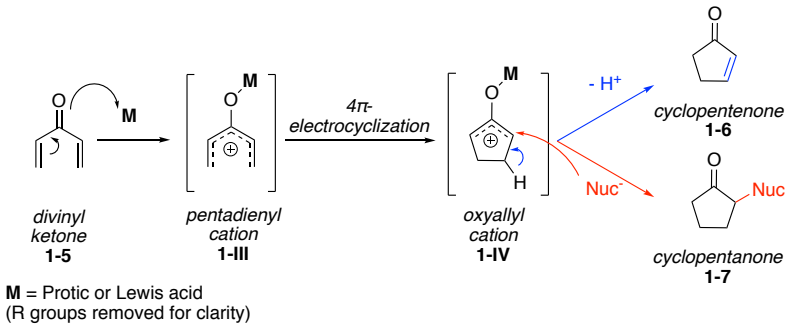


Scheme 1.1 Voländer and Nazarov's Seminal Reports

1.2.1 Nazarov Cyclization Mechanism

In 1952, the mechanism of the Nazarov cyclization was elucidated to proceed through a series of carbocationic intermediates (Scheme 1.2).[6] The reaction proceeds first by exposing a divinyl ketone to either a protic or Lewis acid to activate the substrate, forming a pentadienyl carbocation intermediate. According to the Woodward-Hoffman rules,[7-9] this intermediate undergoes 4π electrocyclization via conrotatory (under thermal conditions) or disrotatory ring closure (under photochemical conditions) to form cyclic oxyallyl cation intermediate, which either by loss of a proton forms cyclopentenone products, or by nucleophilic trapping of the oxyallyl carbocation forms cyclopentanone products. This nucleophilic trapping mechanism is often referred to as the "interrupted" Nazarov cyclization, the focus of a plethora of methodological research. A number of reviews have been written on variants of this reaction, including, but not limited to, the iso-Nazarov reaction,[10] the interrupted Nazarov reaction,[11] catalytic and asymmetric

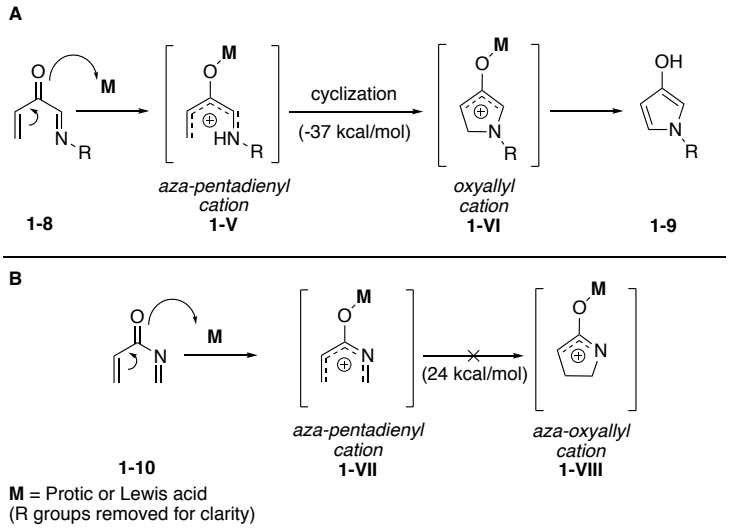
Nazarov reactions,[12-15] the reaction's application toward natural products,[16] combinations of each,[17-22] and other variants.[23-24]



Scheme 1.2 Mechanism of the (Interrupted) Nazarov Cyclization

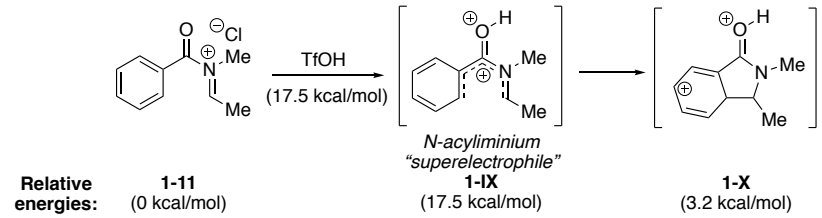
1.2.2 The Aza-Nazarov Reaction

Another well-studied variant of the Nazarov cyclization is the aza-Nazarov cyclization. The term "aza-Nazarov" was first coined in 1997, in Ciufolini's total synthesis of camptothecin.[25] In this variant, when a carbon atom is replaced with a nitrogen atom in the 1-position (Scheme 1.3A), forming hydroxypyrrole products rather than the cyclopentenone products of the Nazarov. Much like the Nazarov, the aza-Nazarov also proceeds through a concerted mechanism to form the oxyallyl cation intermediate through a highly exothermic process (-37 kcal/mol). However, when a carbon atom is replaced with a nitrogen atom in the 2-position (Scheme 1.3B), the reaction becomes endothermic (24 kcal/mol), and the activation barrier toward the concerted mechanism increases greatly (29 kcal/mol), preventing reactivity.[26]



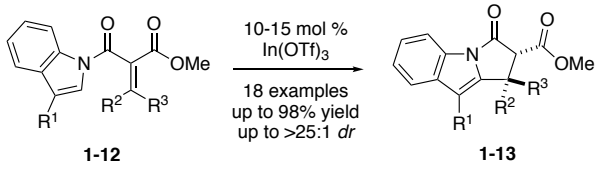
Scheme 1.3 Representative Aza-Nazarov Mechanisms

However, this issue of high activation barrier of aza-Nazarov reactions with nitrogen atoms in the 2-position has been overcome in the past by the use of the highly reactive *N*-acyliminium intermediates, which, when activated by acids, become "superelectrophiles" (Scheme 1.4).[27-28] One other major difference exists in aza-Nazarov substrates with nitrogen in the 2-position than those with nitrogen in the 1-position. It is not totally understood whether the aza-Nazarov on substrates with nitrogen in the two position proceeds through a concerted mechanism, such as a π-electrocyclization, or through a more polar mechanism, such as Friedel-Crafts-type reactivity. According to Baldwin's rules,[29] 5-endo-trig reactions are disfavored, suggesting a more concerted mechanism. However, the use of these "superelectrophiles" has provided a reliable way to induce an aza-Nazarov reaction with nitrogen atoms in the 2-position.



Scheme 1.4 *N*-Acyliminium "Superelectrophile" Aza-Nazarov Cyclization

One other way around the issue of activation energy in the aza-Nazarov cyclization with nitrogens in the 2-position is the use of *N*-acylated heteroarenes, such as pyrroles and indoles. While this type of reactivity certainly does not proceed via a concerted mechanism, but rather instead via a Friedel-Crafts-type mechanism. In a 2011 report, France and co-workers developed an $In(OTf)_3$-catalyzed Friedel-Crafts cyclization to access pyrrolo[1,2-*a*]indole scaffolds found in many natural products (Scheme 1.5).[30] In this example, $In(OTf)_3$ is used to activate the unsaturated malonamide derivative **1-12**, inducing an intramolecular Friedel-Crafts reaction that proceeds in a Michael addition-like fashion. As a result, the pyrrolo[1,2-*a*]indole products obtained resemble those of what might be considered a formal aza-Nazarov cyclization mechanism. As powerful as this methodology may be to access these scaffolds, it has been underexplored in the realm of natural product synthesis.



Scheme 1.5 France's Intramolecular Friedel-Crafts, Aza-Nazarov Cyclization-Like Strategy

1.3 The Importance of Cyclopropanes

Cyclopropanes remain an important structural motif in a number of natural products. A literature search of the cyclopropane structure on Reaxys yields over 6,800 natural products and pharmaceuticals containing the three-membered ring. However, the smallest carbocycle is not only important in natural product synthesis, but methodologically as well, due to its inherently high C-C bond dissociation energy and σ-bond p-character. Cyclopropanes are also the key structural motif found in homo-Nazarov cyclization precursors. Because of their importance in homo-Nazarov cyclizations, it is important to discuss their history, properties, and reactivities to understand their similarities in reactivity to the previously discussed Nazarov cyclizations, and to continue developing these incredibly powerful methodologies to access 6-membered carbocycles.

1.3.1 History and Physicochemistry of Cyclopropane

Cyclopropane was first discovered in 1882 by August Freund upon reacting 1,3-dibromopropane with sodium metal, which then underwent an intramolecular Wurtz reaction to form what was referred to as "trimethylene".[31] Cyclopropane was found to react with elemental bromine and hydrobromic acid to produce 1,3-dibromopropane and 1-bromopropane respectively.[32] This reactivity represented very similar reactivity to olefins. Cyclopropane, along with ethylene oxide, was also found to produce interesting C-C vibrational frequencies (1623 cm^{-1}) similar to, but just outside, known C=C vibrational frequencies in known Raman and IR spectra (~1600 cm^{-1}).[33-37] From this point forward, cyclopropane's true structure became a hotly debated topic in the synthetic community.

1.3.1.1 Pauling's Proposal of "Bent" Bonds

In 1931, Linus Pauling began investigating the nature of chemical bonds, proposing that chemical bonds are a hybridization of s- and p-orbitals, which, in simple molecules like methane, would give H-C-H bond angles of 109.5 degrees. In this report, Pauling also proposed that ethylene was composed of "bent" bonds in which most of the electron density resided outside the internuclear plane.[38] Pauling later expanded upon his original report, quantitatively relating bond energies to the hybridization of their orbitals.[39] Pauling's model at the time, however, was insufficient at explaining bonding regimes in three membered cyclic structures, such as cyclopropanes and epoxides, having cyclic bond angles of 60 degrees. This angular strain combined with the torsional strain of eclipsing C-H bonds contribute to the high ring strain (27.5 kcal/mol) of cyclopropane. Using Pauling's hybridization model, the smallest bond that could be formed are four-membered cyclic scaffolds with C-C bonds consisting s- and p-orbitals at a minimum angle of 90° (composed of only p-orbitals).[40]

1.3.1.2 The Coulson-Moffitt and Walsh Models of Cyclopropane

Pauling's hybridization theory would lead to what is known as the valence bond model of cyclopropane, credited first to Förster in 1939.[41] In 1947, Coulson and Moffitt elaborated on Förster's report, proposing a "bent" valence bond model (Figure 1.1A) of cyclopropane based on Pauling's proposed quantum mechanical model of "bent" bonds in ethylene. In Coulson and Moffitt's model, while the angle between carbon atoms are 60°, the angle between orbitals at a carbon atom are 106° (indicating higher p-character, approximately sp^5 hybridization according to Coulson and Moffitt[42], calculated to be

$sp^{3.46}$)[43], much closer to the 109.5° of normal sp^3-hybridized tetrahedral carbon atoms. As a result of this, electron density is held outside of the direct C-C bonds. Because of these "bent" bonds, ring strain is slightly offset, lowering the energy of the species.[44] Consequential to the carbocycle's orbital angles, the H-C-H angles in cyclopropane are 114° (indicating higher s-character, calculated to be $sp^{2.62}$)[43], and C-C bond length of 1.512 Å, compared to typical $C(sp^3)$-$C(sp^3)$ bond lengths of 1.535 Å. This gives some explanation as to why the strain energy of cyclopropane (27.5 kcal/mol) is only slightly higher than that of the next smallest ring, cyclobutane (26.3 kcal/mol). While this model provides a good explanation for most of electron density lying outside the C-C triangular plane, it does not explain the electron density contained in the center of the ring (to be discussed in following paragraphs).

Also in 1947, a second model began to emerge; Walsh began extensively investigating the structure of cyclopropane molecules influenced by molecular orbital (MO) theory, first proposing a dative bonding model of ethylene to a methylene (Figure 1.1B), citing the H-C-H bond angles of ~120° as evidence.[45] Although this was not the first dative bonding model proposed,[46] Walsh was met with heavy criticism,[47-48] especially due to the known Raman and IR spectra of cyclopropane and ethylene oxide which showed vibrational frequencies outside known C=C vibrational frequencies. Walsh later explained what is known today as the Walsh cyclopropane model, involving three sp^2-hybridized carbon atoms bonding centrally and via very small overlap among the three carbon's 2p orbitals (Figure 1.1C).[49] While Walsh's model was heavily criticized for the initial dative representation, his later corrections eventually led to a good explanation for the presence of electron density in the center of the cyclopropane ring.

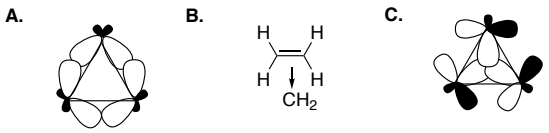


Figure 1.1 Coulson-Moffitt Model vs. the Walsh Model of Cyclopropane

Transposing Walsh's model to a true molecular orbital model (Figure 1.2), cyclopropane consists of three bonding orbitals and three antibonding orbitals. The lowest occupied molecular orbital consists of three sp^2-hybridized carbons overlapping directly at the center of the cyclopropane, where a large amount of electron density dwells. The two degenerate highest occupied molecular orbitals (HOMOs) are made up of two p-orbitals, pointing directly toward one another, overlapping with a node at the third carbon and the three p-orbitals, again pointing directly at one another, overlapping with a node in the midst of a C-C bond. The lowest unoccupied molecular orbital (LUMO) is comprised of three p-orbitals pointing directly at each other with a node between each of the carbon nuclei.[50] Although Walsh's MO model has been heavily criticized, both the HOMOs/LUMO of cyclopropane consisting of p-orbitals rather than the sp^x-hybridized bonding pattern of typical aliphatics in his model and the Coulson-Moffitt model's interpretation of C-C bonds having higher p-character provide good explanation for cyclopropane's often olefinic behavior.

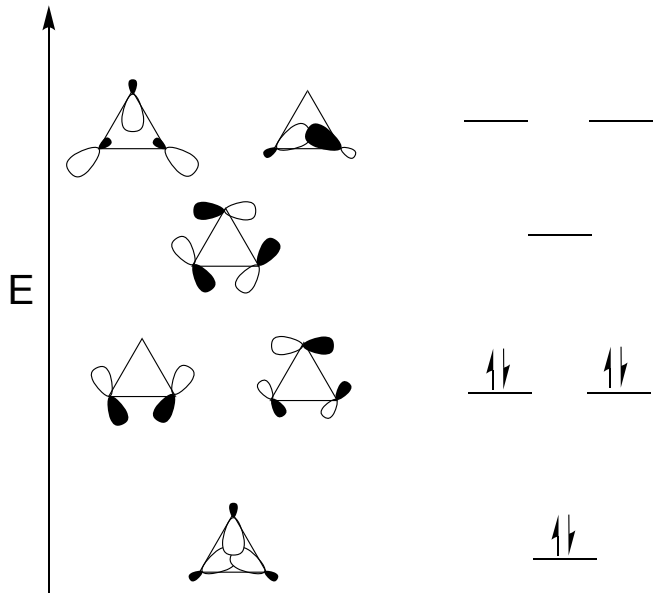


Figure 1.2 Molecular Orbitals of Cyclopropane

1.3.1.3 Cyclopropane and σ-Aromaticity

Although the dative bond model was originally proposed by Dewar,[46] he later proposed a supplementary model to Walsh's MO model, implying that cyclopropane is a σ-aromatic molecule.[51] This idea was proposed as a rationalization for the very small difference in strain energy in cyclopropane and cyclobutane (27.5 vs. 26.5 kcal/mol, respectively), proposing that its aromatic character significantly stabilizes the small carbocycle. Using the 4n+2 equation, cyclopropane consists of a cyclic, six electron array in σ-aromaticity. The concept of σ-aromaticity arises by viewing the bonding electrons of cyclopropane as non-localized (unlike typical σ-bonds) where a two-electron "surface orbital" occupies the center of the three carbons.[52-53] Beyond the low strain energy, this proposal may help explain cyclopropane's upfield shifted protons versus normal aliphatic protons and its reactivity toward electrophiles.[54] This model, much like Walsh's model,

has been met with much skepticism, mostly due to the lack of consistent literature values for stabilization energy and no direct method of measuring stabilization energy.[43]

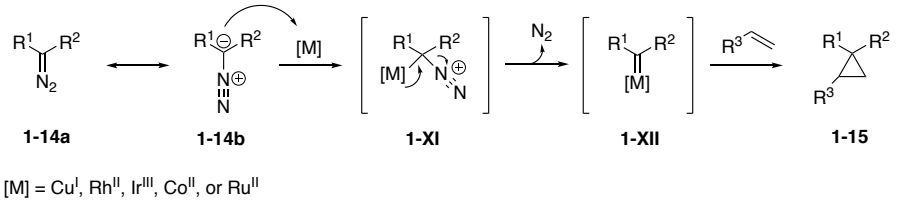
1.4 Synthesis of Cyclopropanes

Key to the understanding of the reactivity of cyclopropanes is the ability to synthesize them. While many beautiful and elaborate syntheses of these strained carbocycles have been accomplished both racemically and stereoselectively,[55-56] most syntheses fall within three major paradigms: (1) synthesis via metal carbenoids from diazo degradation, (2) synthesis via zinc carbenoids from diiodomethane, or (3) synthesis via heteroatom-ylide generation.

1.4.1 Synthesis of Cyclopropanes Via Metal Carbenoids from Diazo Degradation

One of the most popular methods to generate cyclopropanes falls under the category of diazo degradation to form metal carbenoids, which then react with alkenes. This methodology has been extensively reviewed over the last several years.[56-59] Mechanistically, this reaction first proceeds with nucleophilic attack from the diazo carbon onto the impending metal center (usually Cu^{I} or Rh^{II}, though other metals have been used)[60-62] to form a resulting tertiary diazonium intermediate. After eliminating nitrogen gas from collapse of the metal's electrons, a metal carbenoid forms.[63] This carbenoid, when in the presence of an alkene, undergoes concerted addition to the double bond, regenerating the metal catalyst and forming a cyclopropane (Scheme 1.6).[57] Because this reaction proceeds in a concerted fashion, a number of groups have designed catalysts and published methodologies to form cyclopropanes stereoselectively.[55, 64] This is the favored method for cyclopropane formation in the following thesis due to a number

of characteristics: (1) high functional group tolerance, (2) low catalyst loadings (0.1 to 5 mol % with Rh^{II} catalysts),[65] (3) high reaction speed, and (4) ease of setup.

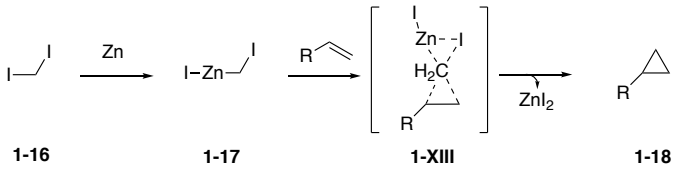


Scheme 1.6 Mechanism of Cyclopropane Formation from Diazo Degradation

1.4.2 Synthesis of Cyclopropanes Via Zinc Carbenoids from Diiodomethane

Another popular method for cyclopropane formation is the reaction of zinc metal or diethylzinc with diiodomethane to form zinc carbenoids, more commonly known as the Simmons-Smith cyclopropanation.[66] In this pathway, zinc metal (or a dialkylzinc) inserts into a single C-I bond of diiodomethane, forming an organozinc intermediate. Although the mechanism of this pathway has yet to be fully elucidated, the organozinc intermediate is suspected to attack via a "butterfly" transition state, releasing zinc iodide and the resulting cyclopropane (Scheme 1.7).[67] The Simmons-Smith cyclopropanation can also be performed asymmetrically, due to the ability of organozinc to coordinate to neighboring heteroatoms and through the use of chiral ligands.[68] A number of other zinc reagents have been developed, including those to induce reactivity for unreactive olefins (Shi's modification)[69-70] and bench-stable zinc carbenoids (Charette's modification).[71] Although Simmons-Smith cyclopropanations are a very highly functional group tolerant method, this method was disfavored for cyclopropane generation in this thesis due to stoichiometric amounts of zinc dust or pyrophoric diethylzinc required and the very high

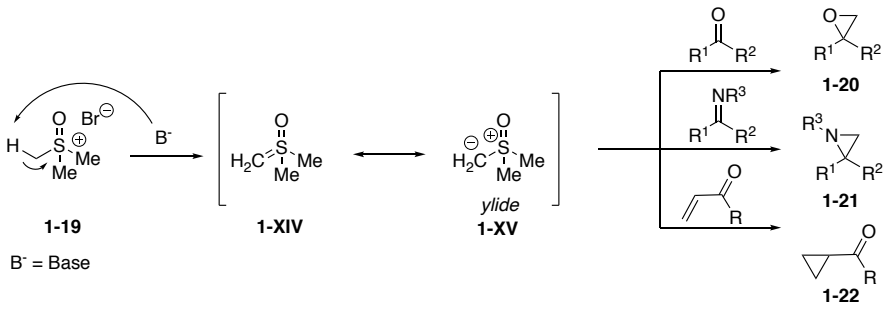
Lewis acidity of the zinc iodide byproduct, which could potentially promote ring-opening of the highly polarized cyclopropanes used throughout this thesis.



Scheme 1.7 Formation of Cyclopropanes Via the Simmons-Smith Method

1.4.3 Synthesis of Cyclopropanes Via Heteroatom-Ylide Generation

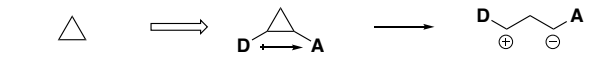
The final major method of the synthesis of cyclopropanes that will be discussed is that using heteroatom-ylides as intermediates. More widely known as the Corey-Chaykovsky reaction, this method uses a base to deprotonate a sulf(ox)onium salt to form the resulting sulf(ox)onium ylide. This ylide is used to nucleophilically attack highly polarized double bonds, such as carbonyls, imines, and Michael acceptors to form epoxides, aziridines, and cyclopropanes, respectively (Scheme 1.8).[72-73] This methodology has been particularly important in natural product total synthesis, including Danishefsky's synthesis of taxol.[74] A number of variants of this reaction have also been developed, including those using ammonium ylides,[75] telluronium ylides,[76-78] and catalytic, asymmetric variants.[79-82] This method was chosen for a number of cyclopropane substrates utilized in this thesis, especially for those in which the alkene degraded under Rh-carbenoid cyclopropanation conditions or were otherwise incompatible.



Scheme 1.8 Synthesis of Cyclopropanes Using Sulfoxonium Ylides

1.5 Donor-Acceptor Cyclopropanes

As previously discussed, cyclopropanes are high-energy species with reactivity that is often analogous to that of olefins. However, as high in energy as cyclopropanes are, they are generally not quick to react to form new entities. In order to increase the kinetic reactivity of cyclopropanes, adding substituents on carbon atoms can induce a bond polarization, decreasing its activation energy.[83-84] Attaching an electron donor and an electron acceptor vicinally across a C-C bond produces what are known as donor-acceptor cyclopropanes (DACPs). This substitution pattern creates an electronic "push-pull" effect along a cyclopropyl C-C bond, resulting in high bond polarization and ready heterolytic cleavage of the species, forming a zwitterionic 1,3-dipolar intermediate (Figure 1.3).



D = electron donor
[OR, SR, NR_2, CH_2SiR_3, vinyl, (hetero)aryl, alkyl]
A = electron acceptor
[CO_2R, COR, CN, CNR, CSR, SOR, SO_2R, $PO(OR)_2$, NOR, NO_2]

Figure 1.3 Bond Polarization in DACPs

Although bond polarization has only been discussed qualitatively until this point, the effect of donors and acceptors in DACPs has been computationally studied to quantify said effects by Werz and coworkers.[85] After testing over 70 combinations of electron donors and acceptors, it was concluded that when one of the two substituents becomes increasingly electron donating and the other substituent is increasingly electron withdrawing, transition state energies decrease. Continuing to add donors and acceptors vicinally across C-C bonds further increases bond polarization, therefore decreasing activation energy (Figure 1.4).[84]

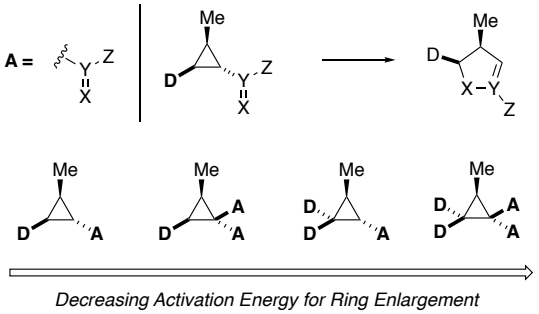


Figure 1.4 Effect of Increasing Bond Polarization on Activation Energy

To this end, a number of groups have sought out DACPs as tools for developing new synthetic methodologies (Figure 1.5) and toward the syntheses of natural products, such as bruguierol,[86] goniomitine,[87] and the formal synthesis of platensimycin[88] (Figure 1.6). In 2005, Pagenkopf and co-workers published a review of DACPs, covering their formation, Lewis acid-mediated reactions, and formal [3+2]-cycloaddition reactions.[89] In 2014, Werz and co-workers published an extensive review covering the use of DACPs in a number of intermolecular reactions, including ring-opening reactions and cycloadditions, with some time spent discussing rearrangements.[83] Soon after, France and co-workers also published another review discussing the use of DACPs in intramolecular

ring-opening cyclization reactions, covering cycloisomerizations, formal cycloadditions, umpolung reactions, rearrangements, ring-opening lacton-/lactamizations, and their application in natural product syntheses.[84] Another authority on cyclopropanes, Jérôme Waser, published a review covering cyclization reaction and annulations of aminocyclopropanes.[90] Pagenkopf also recently reviewed the ability of DACPs to undergo cycloaddition reactions with nitriles.[91] With all of this in mind, it should suffice to state that DACPs a great methodological tool to the synthetic organic community.

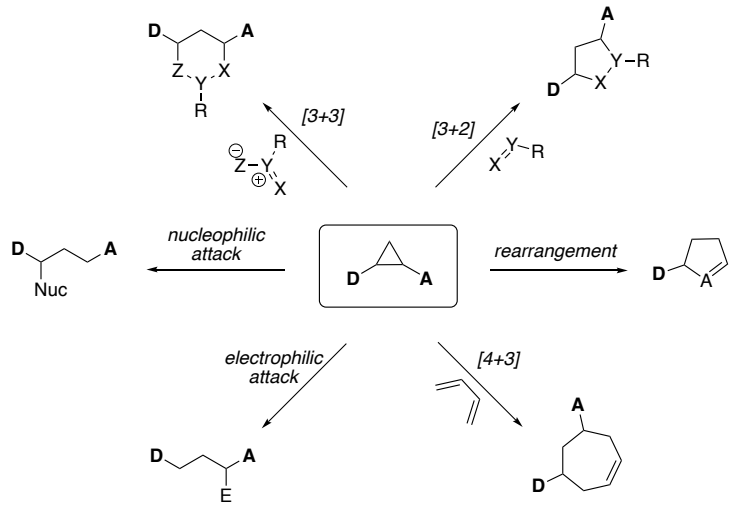
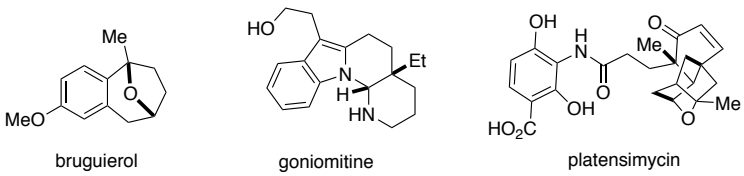


Figure 1.5 Various Reactivities of DACPs

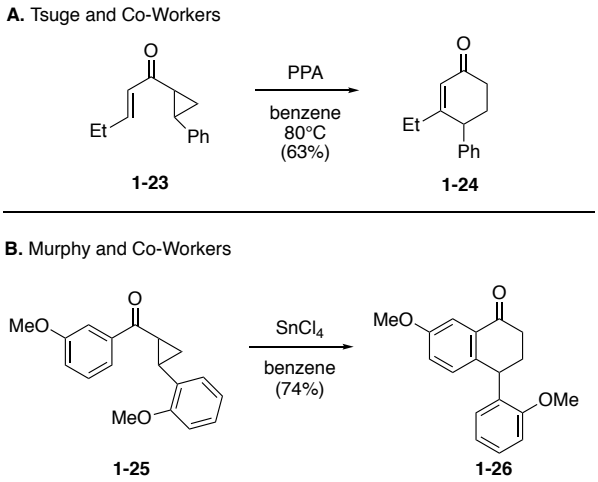


bruguierol goniomitine platensimycin

Figure 1.6 Selected Natural Products Synthesized using DACPs

1.6 The Formal Homo-Nazarov Cyclization

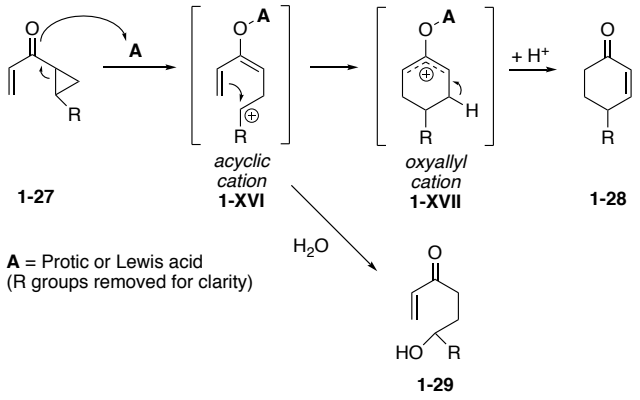
One other powerful methodology not discussed so far involving DACPs is the ring expansion methodology formal homo-Nazarov cyclizations. The term "homo-Nazarov" was first used by Tsuge and co-workers in 1988 when they reported an acid-catalyzed ring expansion of cyclopropyl vinyl ketones to form cyclohexenones (Scheme 1.9A).[92] While this was the first use of this terminology, the ring-opening/ring-closing reactivity of cyclopropyl ketones to form cyclohexenone products was first published in 1980 by Murphy and co-workers (Scheme 1.9B). In this example, cyclopropyl aryl ketones were exposed $SnCl_4$ to form aryl-fused cyclohexanones in up to 80% yield.[93-94]



Scheme 1.9 Early Examples of the Homo-Nazarov Cyclization

While unnamed at the time, the first investigation of the mechanism of the formal homo-Nazarov cyclization was published by Murphy and co-workers in 1982,[95] with Waser and co-workers conducting another mechanistic study in 2009.[96] Upon activation of the cyclopropyl vinyl ketone by a Brönsted or Lewis acid, the cyclopropane ring opens to form an acyclic carbocation, which is subsequently intercepted by the adjacent aryl or

vinyl group to form an oxyallyl cation. This oxyallyl cation is then quenched via elimination by removal of an adjacent proton, forming the cyclohexenone product. However, in the presence of water, the acyclic cation is trapped to form a γ-hydroxyketone, confirming this polar mechanism; this is the origin of the "formal" preceding the homo-Nazarov cyclization name.



Scheme 1.10 Mechanism of the Formal Homo-Nazarov Cyclization

Since Tsuge and co-worker's first use of the "homo-Nazarov" terminology, further exploration of this reactivity was not published until some 20 years later, when Yadav reported the synthesis of 2,3-heteroaromatic-fused cyclohexanones via the ring opening of DACPs.[97] After this report, a plethora of publications began to appear in the literature on these ring-opening/ring-closing cyclizations of cyclopropyl vinyl (or aryl) ketones. In 2009, Waser and co-workers reported the first catalytic homo-Nazarov cyclization using 20 mol % TsOH with cyclopropyl vinyl ketones; however, substrates were limited to activated olefins and heteroarenes as interceptors of the acyclic cation.[98] Soon after, France and co-workers reported the first Lewis acid-catalyzed formal homo-Nazarov cyclization utilizing donor-acceptor-acceptor cyclopropanes with 30 mol % $In(OTf)_3$, and expanding the scope of the reaction to include unactivated olefins as

acyclic cation interceptors.[99] In 2011, Waser further expanded the scope to include heteroatom-activated cyclopropanes with a number of heteroarenes as the representative olefin.[100] Since this time, a number of other reports on formal homo-Nazarov methodology have been published, including a formal homo-Nazarov protocol of alkylidene cyclopropanes,[101] an allylsilane-interrupted formal homo-Nazarov cyclization,[102] a tandem, bicatalytic, cyclopropanation/formal homo-Nazarov cyclization in continuous flow,[103] a formal homo-Nazarov protocol toward tetrahydroindolizines,[104] and an asymmetric formal homo-Nazarov protocol toward enantioenriched dihydronaphthalenes.[105] France and co-workers also published a review highlighting the formal homo-Nazarov cyclization as an incredibly useful synthetic tool toward diversity-oriented synthesis.[106] With all of these recently developed methodologies, it is no wonder that the formal homo-Nazarov cyclization is a powerful synthetic tool; a majority of this thesis will continue to investigate the formal homo-Nazarov cyclization, focusing on further exploring the chemical space, investigating catalysis with DACPs, and expanding the scope of substrates to be used with this methodology.

1.7 Structure of Dissertation

The following dissertation explores novel methodologies using DACPs to access complex, polycyclic molecular scaffolds found in natural products and pharmaceutically relevant compounds. The thesis can be seen as focusing on two major areas; the first area that will be explored is the development of a novel homo-Nazarov cyclization methodology. The second area is the synthesis of two bioactive natural products, the anticancer molecule Propolisbenzofuran B, and the antimalarial Flinderole A. Two appendices to the thesis are also attached, which focus on the development of a

dehydrative Nazarov methodology, and a study on the effects of substituents on the formation of α-alkylidene-γ-butyrolactones (ABLs) from a dehydrative, ring-opening cyclization of cyclopropanes.

Chapter 2 will focus on the development of the novel catalytic, interrupted formal homo-Nazarov cyclization using DACPs and allylsilanes. Included in this chapter will be a discussion of the importance of oxyallyl cations within methodological research and natural product synthesis over the last several years. Also included will be a discussion of the limitations and focus of prior literature on the subject. This chapter will demonstrate an attempt to achieve catalysis and chemodivergence from identical starting materials in the homo-Nazarov cyclization and the limitations of this approach. Two intermolecular oxyallyl cation trapping nucleophiles have been studied thus far: allylsilanes and (hetero)arenes. Ongoing efforts to effect an intramolecular variant toward highly complex polycyclic scaffolds will also be discussed.

Chapter 3 will center on a new approach toward the anticancer natural product Propolisbenzofuran B. The bioactivity of the molecule will be discussed and the previous approach toward synthesizing the molecule and its limitations will be addressed. In our two attempts thus far, DACPs and homo-Nazarov cyclization methodology are used to achieve the synthesis of the cyclohexyl/benzofuran-fused core of the molecule. The limitations of our previous attempt to synthesize the molecule will be discussed, and a new linear sequence toward addressing those limitations will be revealed.

In Chapter 4, a new approach toward the synthesis of the antimalarial natural product Flinderole A will be shown. In our approach, we attempt to utilize a Nazarov-like, Friedel-Crafts methodology, using a novel unsaturated α-sulfonylamide as

precursor. Using this method, we attempted a route geared toward achieving molecular diversity and synthesized a library of analogs for structure-activity relationship studies. Within this chapter will be a discussion of the limitations of previous methodologies toward the molecule and how we sought to address them.

Chapter 5 will summarized all of the previous chapters discussed. Also as part of this chapter, a number of novel strategies will be proposed as a follow-up to the methodology discussed. A number of further steps to achieve the syntheses of the natural products in the thesis will also be proposed.

After the conclusion of the thesis, two appendices will be discussed. In the first appendix, a novel dehydrative Nazarov cyclization approach toward cyclopenta[*b*](hetero)aromatics will be discussed, specifically focusing on the synthesis of the Nazarov precursors, unsaturated β-hydroxy-(hetero)aromatic esters, and the effects of time on the selectivity of the reaction. The second appendix will discuss a novel dehydrative, ring-opening reaction of cyclopropanes to form ABLs. Within this discussion will be a particular focus on substituent effects on *E/Z* selectivity in the ABL products.

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CHAPTER 2. CATALYTIC AND CHEMODIVERGENT INTERRUPTED HOMO-NAZAROV CYCLIZATION REACTIONS [†,‡]

2.1 Oxyallyl Cations: A Handle for Chemical Diversity

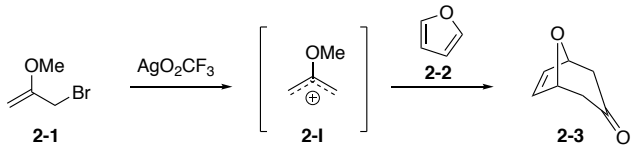
Oxyallyl cations remain a valuable synthetic tool to the synthetic organic community due to their electrophilic nature and ease of accessibility. Researchers were originally interested in allyl cations as a means to generate 7-membered carbocycles, via [4+3]-cycloadditions, due to the cycloadditions pathways toward 5- and 6-membered rings through [3+2]-cycloadditions of allyl anions with dienophiles and [4+2]-cycloadditions of dienes with dienophiles, respectively. Allyl cations were known to be much harder to access, reacting with solvent upon generation, and other more stable allyl cations polymerizing.[1] Oxyallyl cations, on the other hand, provide greater stability and more controlled reactivity. Although oxyallyl cations may have originated in the late 19th century with the first Favorskii reaction,[2] research into the reactivity of the intermediate itself did not take place until 1962, when Fort reported the methanolysis of α-chloro-dibenzylketone.[3] In this initial report, Fort proposed an elimination-addition mechanism promoted by 2,6-lutidine. It was not until later that Fort obtained more concrete evidence for the oxyallyl intermediate when he reported its capture with furan via a [4+3]-cycloaddition.[4] Since this report, a number of methods for the generation and utility of oxyallyl cations have been published.

[†] Allylsilane trapping studies done in collaboration with Raynold Shenje and Katherine M. Francois. Published in *Org. Lett.* **2014**, *16*, 6468-6471.

[‡] (Hetero)aryl trapping studies done in collaboration with Raynold Shenje. Published in *J. Org. Chem.* **2016**, *81*, 8253-8267.

2.1.1 Generation of Oxyallyl Cations

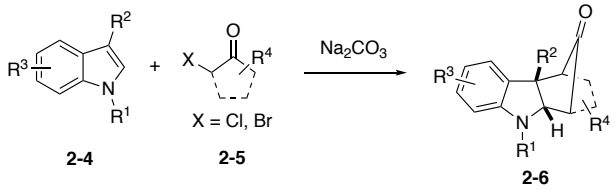
There are many different methods to generate oxyallyl intermediates, while three tend to stand out above all others: (1) heterolytic cleavage of 2-alkoxyallyl halides, (2) enolization of α-haloketones, and (3) metal reduction of α,α'-dihaloketones. The first mentioned method, heterolytic cleavage of 2-alkoxyallyl halides, generally uses silver salts as a method of halogen abstraction to generate oxyallyl cations. The first example of this method came only ten years after Fort's seminal report, published by Hoffman. In his report, Hoffman used silver trifluoroacetate to generate a methoxyallyl cation, which subsequently underwent a [4+3]-cycloaddition with furan to form the bicycle shown in Scheme 2.1.[5] Since Hoffman's report, this remains one of the most reliable methods to generate oxyallyl cations to date.



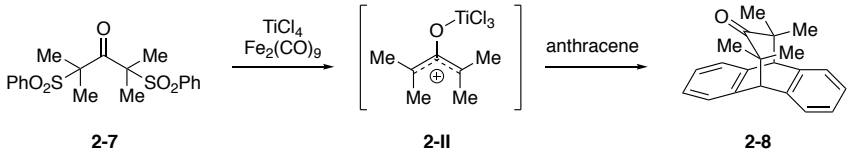
Scheme 2.1 Hoffman's Seminal Work with Oxyallyl Cations

The second method, using acids or bases to generate oxyallyl cations from α-haloketones, also remains a popular method. The first example of a [4+3]-cycloaddition with oxyallyl cations was Fort's original report, in which he used 2,6-lutidine to generate the oxyallyl to be captured by furan.[4] In a more recent example, Wu and co-workers reported a Na_2CO_3-promoted [3+2]-cycloaddition of electron-rich 3-substituted indoles with α-haloketones (Scheme 2.2).[6] Base-promoted methods have also been useful in the transformations of azaoxyallyl cations.[7-10] Alternatively, Lewis acids can also be used as promoters, such as in Hardinger's example, where α,α'-bisulfonylketones are treated

with $Fe_2(CO)_9$ and $TiCl_4$ to generate oxyallyl cations, which are subsequently reacted with alkynes to form cyclopentenones (Scheme 2.3).[11]

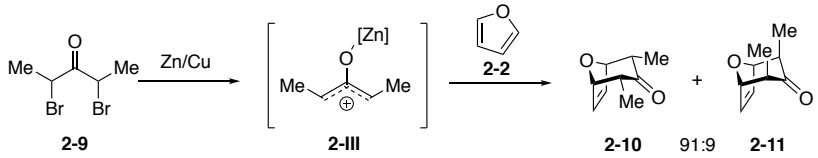


Scheme 2.2 Wu's Base-Mediated [3+2]-Cycloaddition



Scheme 2.3 Harbinger's Lewis Acid-Activated Bissulfonylketones as Oxyallyl Precursors

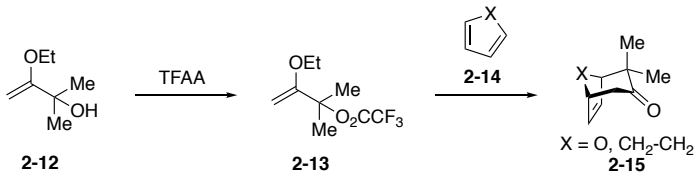
The third method of generating oxyallyl cations relies on metals to reduce α,α'-dihaloketones. In this method two one-electron reductions occur, typically using zinc dust, at one of the α-positions of the dihaloketone. The first reduction generates a radical cationic intermediate, which is subsequently reduced to form an enolate. The second halogen is abstracted by the metal salt to form oxyallyl cations (Scheme 2.4). Several chemists have relied on this method to generate oxyallyl cations, including Hoffman,[12] Noyori,[13] and Mann.[14]



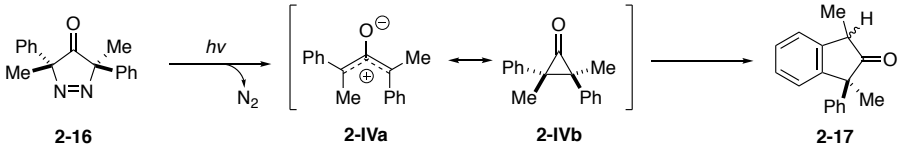
Scheme 2.4 Zinc Reduction of Dibromoketones to Form Oxyallyl Cations

While the three previously mentioned methods are some of the most reliably used to generate oxyallyl cations, many other elaborate and beautiful methods have been

published over the last few decades. The anhydride-mediated activation of α-hydroxy alkyl vinyl ethers as used is another method developed by Hoffman[15-16] (Scheme 2.5) that went on to be used in the total synthesis of aphanamol.[17] In this method, an allyl trifluoroacetate is generated with TFAA from allyl alcohol **2-12**. Upon heating with a diene, the oxyallyl cation is generated and undergoes a [4+3]-cycloaddition to form bicyclic scaffolds of the type **2-13**. One other method for the generation of oxyallyl cations is the photolytic degradation of 3,3,5,5-tetraalkyl- or 3,5-dialkyl-3,5-diaryl-3,5-dihydro-4*H*-pyrazol-4-ones via the release of nitrogen gas. This method has been used to generate oxyallyl cations en route to tetrasubstituted cyclopropanones or *cis*-/*trans*-1,3-dialkyl-1-aryl-2-indanones (Scheme 2.6).[18-20] This methodology, although still in its infancy, could potentially become a promising route to oxyallyl cations via a photochemical method rather than other chemical methods.



Scheme 2.5 Hoffman's TFAA-Mediated Generation of Oxyallyl Cations

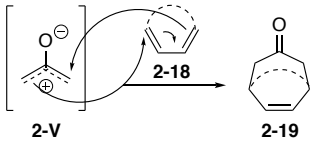


Scheme 2.6 Photochemical Generation of Oxyallyl Intermediates

The final methods, and most relevant to the chapter at hand, to introduce oxyallyl cations in this chapter is their generation within the Nazarov and FHN reactions. Since their origin by these mechanisms was covered previously in Chapter 1.2 and 1.6, they will not be discussed further here.

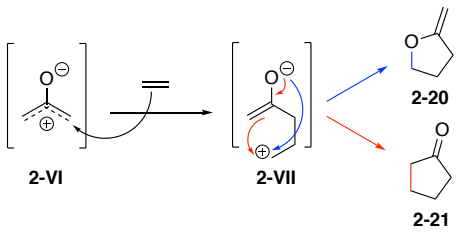
2.1.2 Synthetic Utility of Oxyallyl Cations

The electrophilic nature of oxyallyl cations gives rise to a plethora of reactivity with a vast array of nucleophilic partners. As mentioned a number of times previously, oxyallyl cations readily undergo [4+3]-cycloadditions (Scheme 2.7). To this end, a number of reviews have been written focusing specifically on only this reactivity.[10, 17, 21-25] In this reaction pathway, oxyallyl cations undergo a [4π+2π]-electrocyclization with dienes and (hetero)cyclic dienes, giving rise to seven-membered and bicyclic carbocycles, such as **2-19**. This reaction can proceed either via a concerted or stepwise mechanism, as exhibited in Hoffman's,[26] Noyori's,[27] and Montaña's[28-29] results. It does seem however that diastereoselectivity is dependent upon several factors, including electron deficiency of the oxyallyl cation, the counterion used, and reaction temperature.[30]



Scheme 2.7 Generic Concerted [4+3]-Cycloaddition Mechanism with Oxyallyl Cations

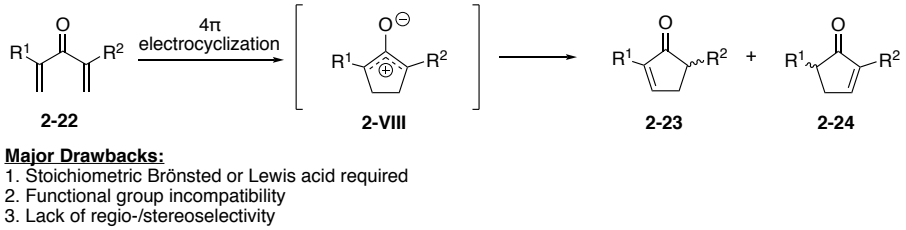
Another powerful use for oxyallyl cations, though much more uncommon, is in [3+2]-cycloadditions.[31] Unlike the [4+3]-cycloaddition, the [3+2]-cycloaddition is not thermally allowed by Frontier molecular orbital theory, resulting in almost exclusively a stepwise mechanism. Also unlike the [4+3]-cycloaddition, oxygen atoms often participate in the reaction, resulting in two major product types: cyclopentenones and saturated furans (Scheme 2.8). Alkynes are also effective partners for [3+2]-cycloaddition reactivity.



Scheme 2.8 Generic Thermal [3+2]-Cycloaddition Mechanism with Oxyallyl Cations

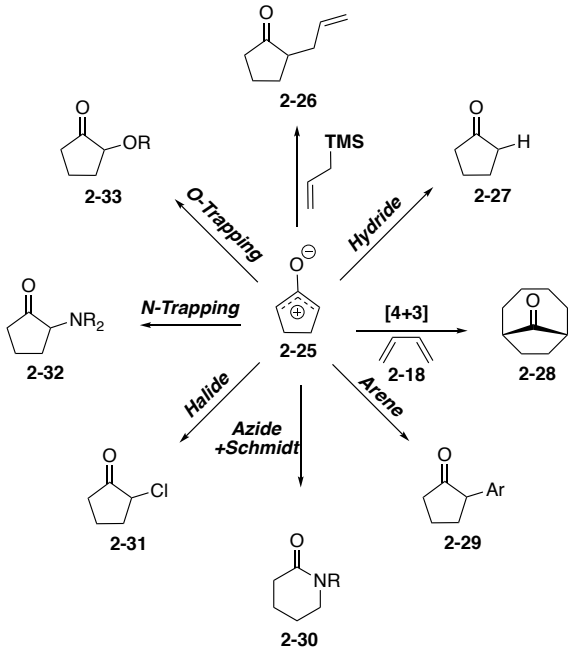
2.2 Previous Nazarov Methodologies

The Nazarov cyclization is a particularly powerful methodology that has led to the formation of very densely functionalized cyclopentenones. As powerful as it may be, the Nazarov previously suffered from several major drawbacks, including (1) the use of stoichiometric to super-stoichiometric amounts of very strong Brönsted or Lewis acids for activation, leading to (2) functional group incompatibility, and (3) lack of regio- and stereoselectivity although a pericyclic 4π-electrocyclization process (Scheme 2.9). The shortcomings of this methodology has been a focal point of several research groups, such as (1) Denmark, who developed a silicon-directed Nazarov cyclization to alleviate regioselectivity issues[32] and later induce enantioselectivity,[33] (2) Tius, who employed electron-donating groups at the α-position of pentadienyl cation precursors toward inducing activation via catalysis,[34] (3) Frontier, who used both electron-donating and electron-withdrawing groups to effect a polarized Nazarov cyclization, leading to catalysis,[35-36] (4) Aggarwal, who published a catalytic, enantioselective process by utilizing electron withdrawing groups at the α-position and chiral Lewis acid complexes.[37]



Scheme 2.9 Drawbacks of Early Nazarov Methodology

Perhaps one of the most influential inspirations for this thesis work came from that of West's group and the exploration of the interrupted Nazarov cyclization. West employed a number of nucleophilic trapping agents to capture the oxyallyl cation of the Nazarov mechanism, including halogens, hydrides, allylsilanes, (hetero)arenes, dienes, olefin cascades, heteroatoms, and azides, leading to unsaturated cyclopentanones, rather than the cyclopentenones of the traditional Nazarov cyclization (Scheme 2.10).[38]



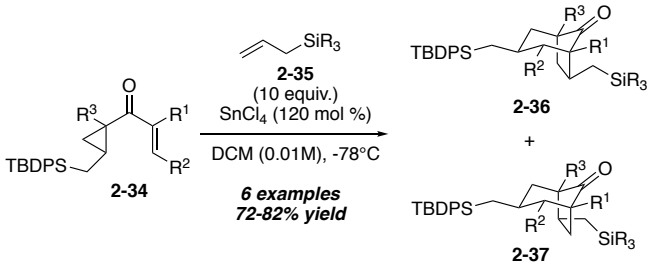
Scheme 2.10 West's Interrupted Nazarov Cyclization Methodologies

2.3 Previous Formal Homo-Nazarov Methodologies

As one might glean from the previous section, the Nazarov reaction of divinyl ketones has been extensively explored, and the breadth of literature on the topic continues to grow. When one replaces one of the vinyl groups with a cyclopropane, a homologous reaction type occurs: the formal homo-Nazarov (FHN) reaction. As discussed extensively in Chapter 1, cyclopropanes have similar reactivity to olefins. From this, one can reasonably assume that cyclopropanes can undergo activation by Brönsted or Lewis acids toward ring-opening cyclization to form six-membered, rather than five-membered, carbocycles. Over the last ten years, dozens of publications have appeared in the literature on this topic covering Brönsted acid-[39] and Lewis acid-catalyzed[40] reactions, the formation of cyclohexanone-fused heteroaromatics,[41] continuous flow FHN chemistry,[42] and several natural product syntheses utilizing the methodology.

With the plethora of FHN chemistry that has been developed, an interrupted variant of the FHN reaction remains underexplored chemical space. In this variant, much like West's interrupted Nazarov, a number of nucleophiles could be used to provide access to a plethora of densely functionalized cyclohexanones, rather than the cyclopentanones of the interrupted Nazarov. Before this work, to our knowledge, only one other publication involving an interrupted FHN variant had been explored. In this publication, Yadav and co-workers revealed an allylsilane-interrupted FHN cyclization using DACPs, 1.2 equivalents of $SnCl_4$, and 10 equivalents of allyltrimethylsilane (Scheme 2.11).[43] Pioneering within its own right, Yadav's methodology was limited in a number of ways: (1) two regioisomers of the bicyclo[3.2.1]octanone product were formed with little selectivity, (2) a stoichiometric amount of the highly corrosive and toxic $SnCl_4$

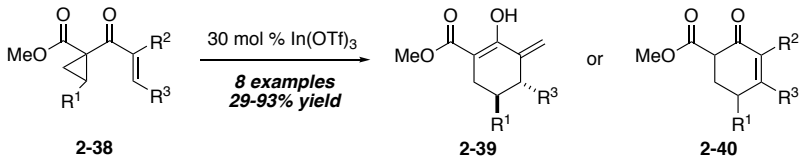
promoter is required, and (3) very limited substrate scope (only eight substrates, six of which used -CH_2TBDPS as a donor). Considering these limitations, there exists a need for a more robust methodology both to alleviate these issues with the interrupted FHN cyclization and to further expand its viability in other synthetic applications.



Scheme 2.11 Yadav's Pioneering Interrupted FHN Cyclization

2.4 The Development of a Catalytic Interrupted FHN Cyclization

Drawing inspiration from previous methodologies developed in the France lab (Scheme 2.12),[40-42] it was hypothesized that adding a second acceptor geminally to the first acceptor group would further polarize the cyclopropane C-C bond, helping to achieve catalytic ring-opening. In doing this, one would then alleviate one of the major issues with previous interrupted FHN methodologies and achieve catalysis. Catalysis also provides a much milder reaction environment, which could lead to better functional group tolerance, and thus, broader substrate scope. It was also hypothesized that adding the second acceptor would polarize the oxyallyl cation, resulting in regioselective attack by nucleophiles. Essentially, by simply adding a second acceptor group, one might be able to alleviate many of the issues associated with the first iteration of the interrupted FHN cyclization.



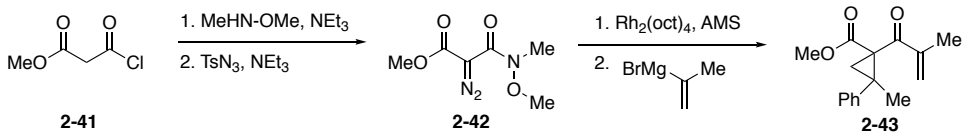
Scheme 2.12 France's Previous Work with Cyclopropyl Vinyl Ketones

2.4.1 Reaction Design

Moving forward with designing a catalytic interrupted FHN cyclization, a moderate electron donor needed to be chosen in order to effect ring opening. Methyl and phenyl substituents were chosen as the donor groups, providing dual stabilization of the ring-opening cation intermediate; the phenyl group provides benzylic stabilization of the cation, and the methyl group creates a tertiary center. 1,3-dicarbonyls were chosen as acceptors due to their ease of accessibility and their ability to form six-membered coordinate complexes with oxophilic Lewis acids. More specifically, esters were chosen because of their ease of removability by Krapcho conditions in these systems, and their ability to induce charge localization of the oxyallyl intermediates.

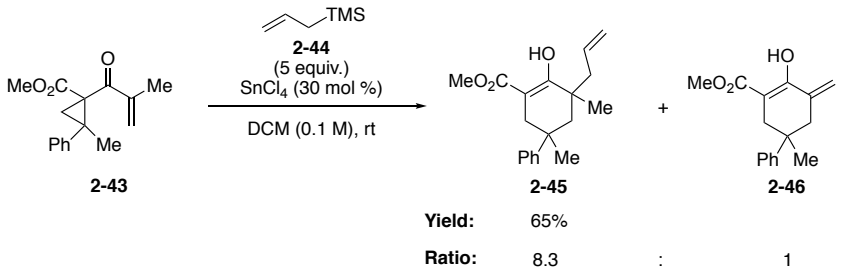
2.4.2 Synthesis of the Model Substrate and Proof of Principle

The model substrate, shown in Scheme 2.13, was synthesized according to the France lab's previously reported protocol.[40] Its synthesis began by treating methyl malonyl chloride with methoxy methylamine and triethylamine to form a Weinreb amide ester, which is then taken forward for diazo transfer using tosyl azide and trimethylamine. The diazo then undergoes a Rh-catalyzed cyclopropanation with α-methylstyrene (AMS), followed by addition of isopropenylmagnesium bromide to give the model substrate.



Scheme 2.13 Synthesis of the Model Donor-Acceptor-Acceptor Cyclopropane

After synthesizing the model substrate, the model cyclopropane substrate was exposed to 30 mol % $SnCl_4$ and 5 equivalents of allyltrimethylsilane in DCM at room temperature. $SnCl_4$ was chosen due to its oxophilic character and strong Lewis acidity. It has also been shown in some of West's previous publications that $SnCl_4$ is tolerant of allylsilanes in interrupted Nazarov reactions.[44] In this initial reaction, the desired allylated, interrupted FHN product was obtained in 65% yield as a keto-enol mixture, but some of the general FHN cyclohexenone product was also obtained (Scheme 2.14). While this provided important proof of concept, the reaction could be improved in two major ways: (1) decreased catalyst loading and (2) increased yield/selectivity toward the desired allylated products.



Scheme 2.14 Initial Allylative Interrupted FHN Cyclization

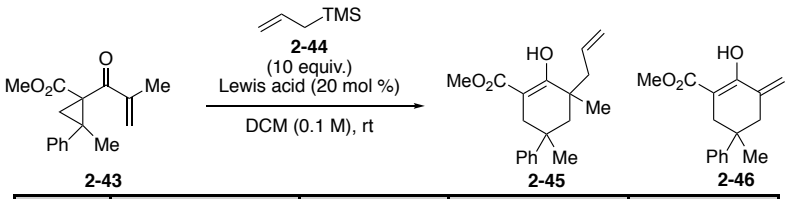
2.4.3 Reaction Optimization

Optimization began with screening a number of Lewis acids at 20 mol % of the Lewis acid, 10 equivalents of allyltrimethylsilane, with the cyclopropane at 0.1 M in DCM. The results of the optimization are contained in Table 2.1. 3+ salts generally gave

moderate yields of the desired allylated product, albeit in reduced yields. 2+ salts favored FHN products over interrupted products. $SnCl_4$ performed the most efficiently, giving the desired allylated product at 75% yield with a chemoselectivity of 17:1 of the desired product to the FHN product. $Sc(OTf)_3$ gave the second highest yield; however, selectivity toward the allylated product was significantly reduced. All other Lewis acids gave significantly lower yields, reduced selectivity, or much longer reaction times.

Because $SnCl_4$ performed best in the catalyst screen, the next screen analyzed catalyst loading (Table 2.2). A series of 30, 20, 15, 10, and 5 mol % were each tested. The screen was conducted with 5 equivalents of allyltrimethylsilane and the model substrate at 0.1 M in DCM. 30 mol % performed best, yielding the allylated product in 51% in one hour. However, 20 mol % gave 42% yield in 24 hours, with slightly higher selectivity. All other loading gave either significantly decreased yields or much longer reaction times. Because 30 mol % loading is indicative of low catalyst turnover, and 20 mol % gave comparable yield with slightly higher selectivity, 20 mol % was carried forward as the optimal loading.

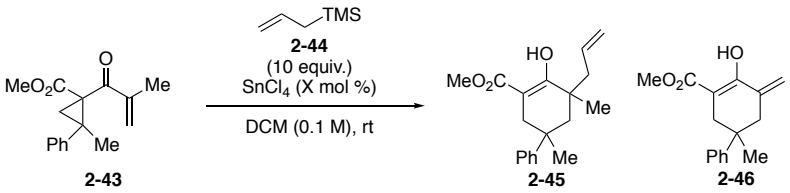
Table 2.1 Lewis Acid Screening



Entry	Lewis Acid	Time (hr)	Yield (%)[a] 2-45	2-45:2-46
1	**$SnCl_4$**	**24**	**75**	**17:1**
2	$TiCl_4$	96	34	1:1.1
3	$In(OTf)_3$	2	41	1.7:1
4	$Sc(OTf)_3$	6	43	4.2:1
5	$Al(OTf)_3$	72	42	6.8:1
6	$Yb(OTf)_3$	70	26	2.3:1
7	$Ga(OTf)_3$	70	12	1:1.3
8	$Sn(OTf)_2$	48	20	1.2.4
9	$Zn(OTf)_2$	48	13	1.2.3
10	$Cu(OTf)_2$	48	11	1:6.7
11	$Mg(OTf)_2$	48	9	1:4.2
12	$InCl_3$	48	28	1:1.5
13	$BF_3 \cdot Et_2O$	70	34	1.1:1

[a] Isolated yields after column chromatography.

Table 2.2 Various $SnCl_4$ Loading



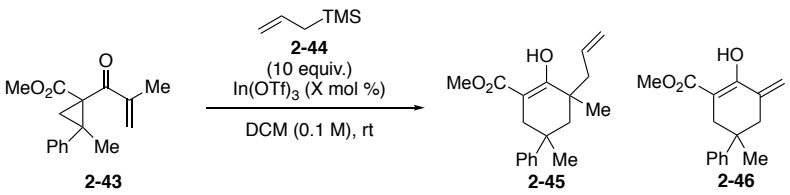
Entry	$SnCl_4$ (mol %)	Time (hr)	Yield (%)[a] 2-45	2-45:2-46
1	30	1	51	1.9:1
2	**20**	**24**	**42**	**2.2:1**
3	15	24	32	2.1:1
4	10	48	24	2.3:1
5	5	48	16	2.8:1

[a] Isolated yields after column chromatography.

Because of the inherent corrosive properties and toxicity of neat $SnCl_4$, the viability of $In(OTf)_3$ as a back-up catalyst (Table 2.3) was screened. $In(OTf)_3$ performed well in the initial screen, giving 41% yield of desired product in 2 hours, although selectivity was quite low. It was hypothesized that decreasing the loading of $In(OTf)_3$

could both increase selectivity and yield. Lowering the loading of $In(OTf)_3$ to 5 mol % did increase reaction time by 17 hours, but increased yield to 63% and selectivity from 1.7:1 to 5.6:1 of the desired product to FHN product.

Table 2.3 Various $In(OTf)_3$ Loading



Entry	$In(OTf)_3$ (mol %)	Time (hr)	Yield (%)[a] 2-45	2-45:2-46
1	20	2	41	1.7:1
2	**15**	**3**	**49**	**4:1**
3	10	5	43	2.7:1
4	5	19	63	5.6:1

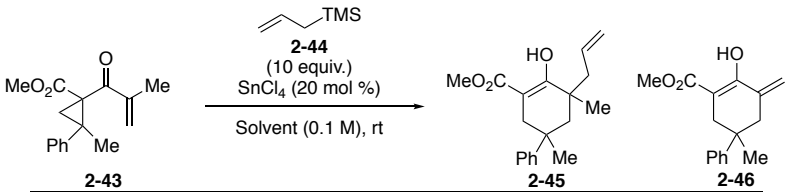
[a] Isolated yields after column chromatography.
[b] Reactions performed at 0.1 M in DCM at room temperature

After determining 20 mol % $SnCl_4$ to be the optimal catalyst and loading, the final screen tested the viability of other solvents in toward this reactivity (Table 2.4). Both polar protic and polar aprotic solvents, THF, and EtOAc provided only decomposition and side products. THF and EtOAc likely coordinated to the catalyst, preventing FHN reactivity. Only chlorinated solvents, hexane, and toluene gave any desired product. All of these solvents provided decreased yields and selectivities compared to DCM, so DCM was chosen as the optimal solvent.

After choosing the optimal solvent, cyclopropane concentration and allylsilane loading was screened (Table 2.5). In this screen, 20 mol % of $SnCl_4$ was used; the indicated loading of allylsilane, and DCM was used as the solvent. Increasing concentration to 1 M drastically decreased reaction time while slightly decreasing yield and significantly reducing selectivity. At 5 equivalents of allyltrimethylsilane, both yield and selectivity are decreased at 0.1 M in DCM. An attempt to increase yield with only 5

equivalents of allyltrimethylsilane by increasing concentration was also conducted. Unfortunately, only decreased reaction times were observed. In conclusion, the optimized conditions were determined to be 20 mol % $SnCl_4$, 10 equivalents of allyltrimethylsilane, and the cyclopropane at 0.1 M in DCM.

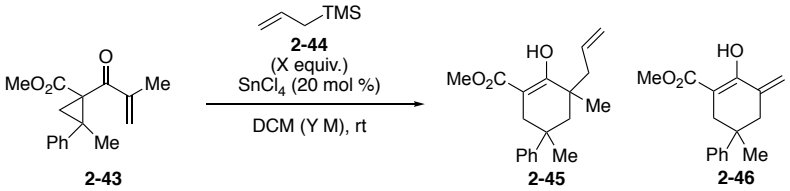
Table 2.4 Solvent Screen



Entry	Solvent	Time (hr.)	Yield (%)[a] 2-45	2-45:2-46
1	MeOH	36	--	--
2	DMF	36	--	--
3	MeCN	10	--	--
4	THF	72	--	--
5	EtOAc	2	--	--
6	1,2-DCE	6	63	6.5:1
7	Hexane	36	20	1.7:1
8	Toluene	36	36	2.3:1
9	**DCM**	**24**	**75**	**17:1**

[a] Isolated yields after column chromatography.

Table 2.5 Concentration and Allylsilane Loading Optimization



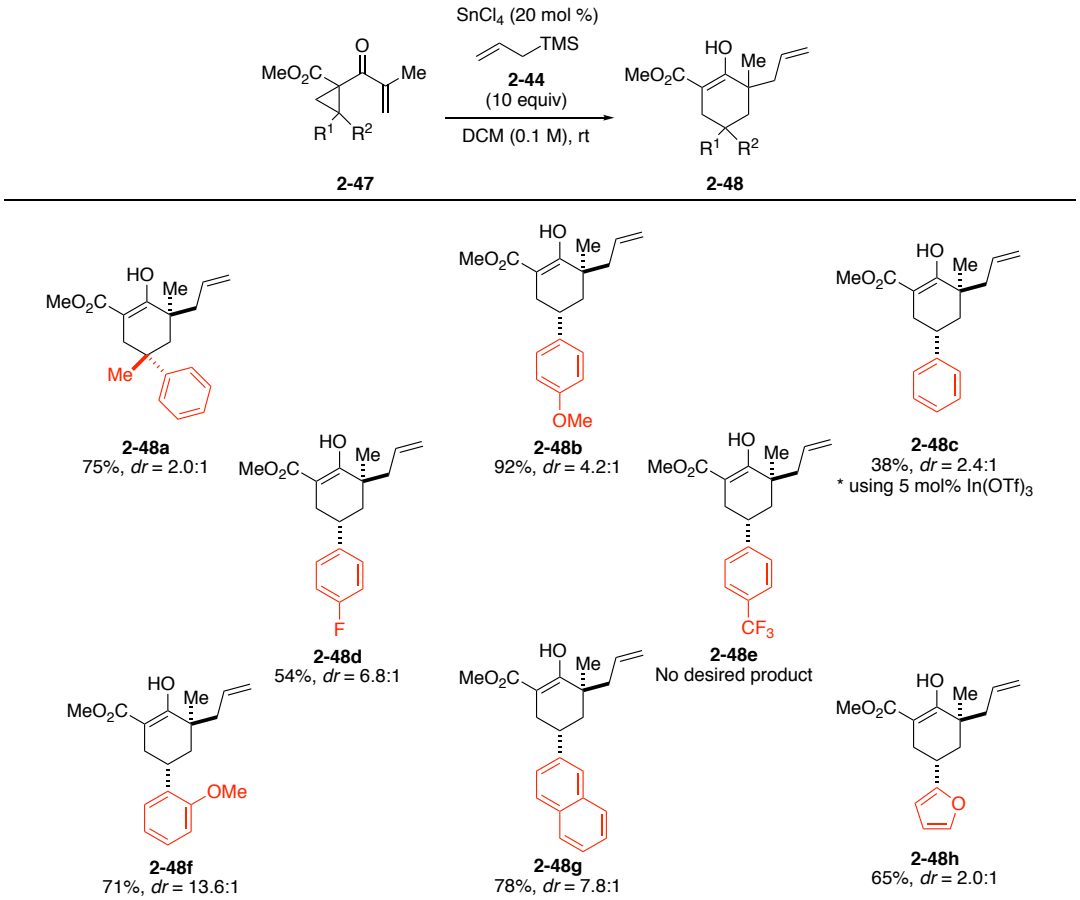
Entry	Conc. (M)	Silane (equiv.)	Time (hr)	Yield (%)[a] 2-45	2-45:2-46
1	**0.1**	**10**	**24**	**78**	**16.7:1**
2	1	10	2.5	60	1.9:1
3	0.1	5	24	59	2.9:1
4	0.3	5	26	47	2.2:1
5	0.5	5	5	42	1.1:1
6	1	5	1	57	2.1:1

[a] Isolated yields after column chromatography.

2.4.4 Reaction Scope

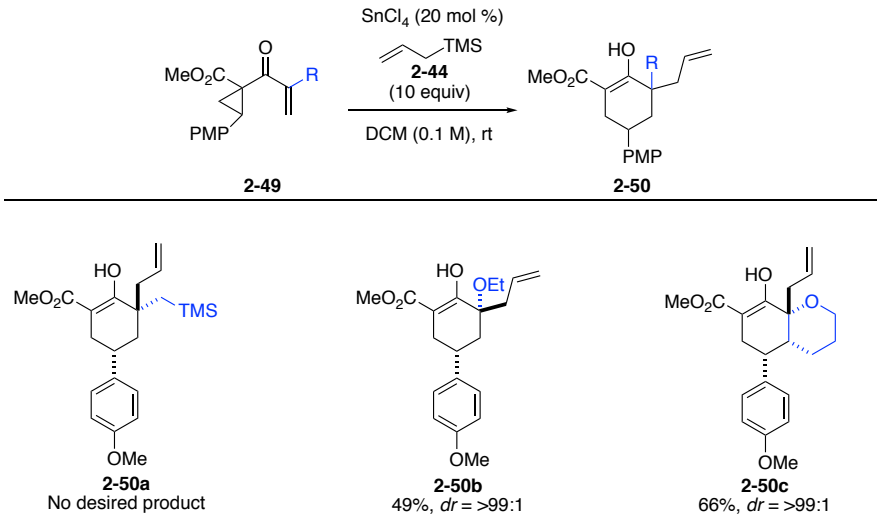
After obtaining the optimized conditions, the scope of differing substrates was investigated. In the course of the examination of scope, some diastereoselectivity was expected. The observed diastereoselectivities could be attributed to product development control, in which the transition state for allylsilane attack is late on the reaction coordinate, and therefore, very product-like.[45-46] In this model, the product with the least torsional strain is produced following allylsilane attack. However, further studies need to be conducted to truly elucidate the origin of the diastereoselectivities.

The first position altered was the donor group on the cyclopropane. The results of this study are contained in Scheme 2.15. The best performing donor was PMP, giving 92% yield and 4.2:1 *dr*. Because of its very strong electron donating ability, this presumably decreases activation energy, thus increasing yield. A simple phenyl donor did not proceed well with $SnCl_4$ as a catalyst, so $In(OTf)_3$ was used instead, yielding 38% of desired product at a 2.4:1 *dr*. Highly electron deficient donors, such as the 4-CF_3-phenyl, did not give any desired product under either $SnCl_4$ or $In(OTf)_3$ conditions, likely due to high activation energy toward ring opening. Heteroaromatic donors were also tolerated, giving moderate yield (65%) and low diastereoselectivity.



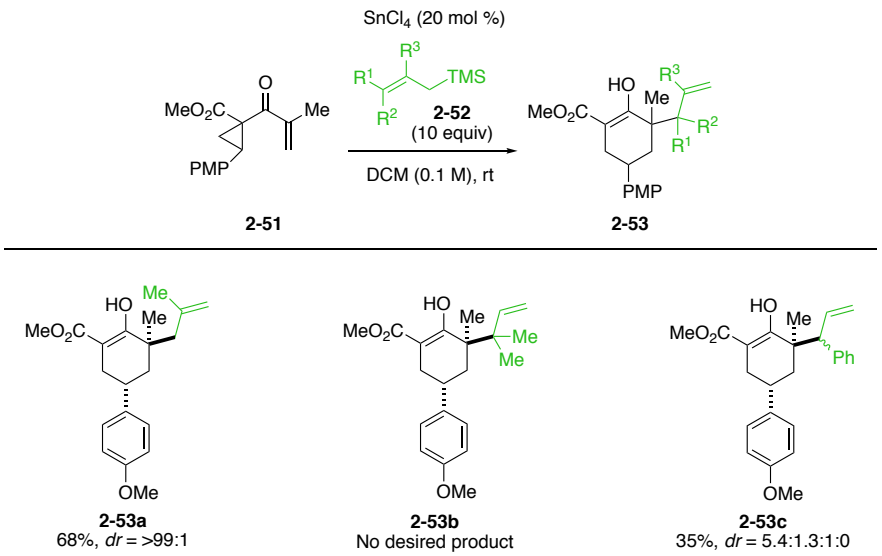
Scheme 2.15 Investigation of the Cyclopropane Donor Group

Next, the effect of different substituents on the vinyl group was investigated (Scheme 2.16). *Para*-methoxyphenyl was chosen as the cyclopropane donor due to the high yield of allylated product. Installing a β-silyl substituent does not provide β-silyl stabilization of the oxyallyl intermediate; it instead yields only FHN product through Hosomi-Sakurai-type elimination. A heteroatom in the α-position, however, gives the desired allylation product, whether through a cyclic or acyclic ether. Yields for these substrates are moderate, but complete diastereoselectivity is observed.



Scheme 2.16 Investigation of Vinylic Substituent Effects

Finally, substituents on the allylsilane were explored (Scheme 2.17). Introducing a methyl group at the β-position to the trimethylsilyl group was well tolerated, giving 68% yield and total diastereoselectivity. Geminal dimethyl allyltrimethylsilane does not give any desired product, presumably due to the large amount of steric hindrance upon oxyallyl attack. Finally, cinnamyl trimethylsilane is tolerated, giving the desired allylated product in 35% yield and a *dr* of 5.4:1.3:1:0. The low yield, much like the germinal dimethyl allyltrimethylsilane, can be attributed to significant steric hindrance toward oxyallyl cation attack.



Scheme 2.17 Investigation of Substituents on Allylsilanes

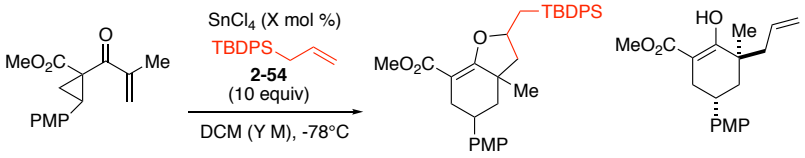
2.5 Chemodivergence in the Interrupted, FHN Cyclization

As part of the study, it was further hypothesized that when bulkier allylsilanes are used, the silyl group could be retained. To begin the study, the optimized conditions were used with the PMP cyclopropyl donor and allyl-TBDPS. In the initial reaction, the temperature was also decreased in an attempt to further slow desilylation. Gratifyingly, the silyl group was retained, although an unexpected hexahydrobenzofuran product was obtained in 20% yield. This *O*-alkylated product is in stark contrast to the formal [3+2] *C*-alkylated product observed by Yadav and coworkers.[43] Neither Yadav's C-alkylated nor allylated FHN product was observed in this study. The lack of *C*-alkylated product is likely due to the polarization of the oxyallyl intermediate, forcing *O*-attack upon the β-silyl stabilized cation. This represented the first example of this reactivity in the F cyclization. Its discovery instigated a further investigation, including optimization of the reaction and probing substrate scope.

2.5.1 *Reaction Optimization*

Due to the initial success of $SnCl_4$ as a catalyst, the first optimization screen investigated its loading using allyl-TBDPS as the allylsilane (Table 2.6). PMP was, again, chosen as the cyclopropane donor due to its efficiency toward the initial allylative, interrupted FHN conditions. Decreasing the concentration five-fold increased yield to 33% and decreased degradation products. Further decreasing the concentration to 0.01 M increased yield slightly more to 37%. Increasing catalyst loading to 50 mol % increases yield to 49% also decreasing the amount of degradation observed. Increasing catalyst loading to 120 mol % drastically increased yield to 69%. Attempts to improve the reaction with other Lewis acids led to decreased yields and significant degradation.

Table 2.6 Optimization of Lewis Acid/Concentration Toward Formal [3+2]-Cycloaddition



2-51 **2-55** **2-48b** not observed

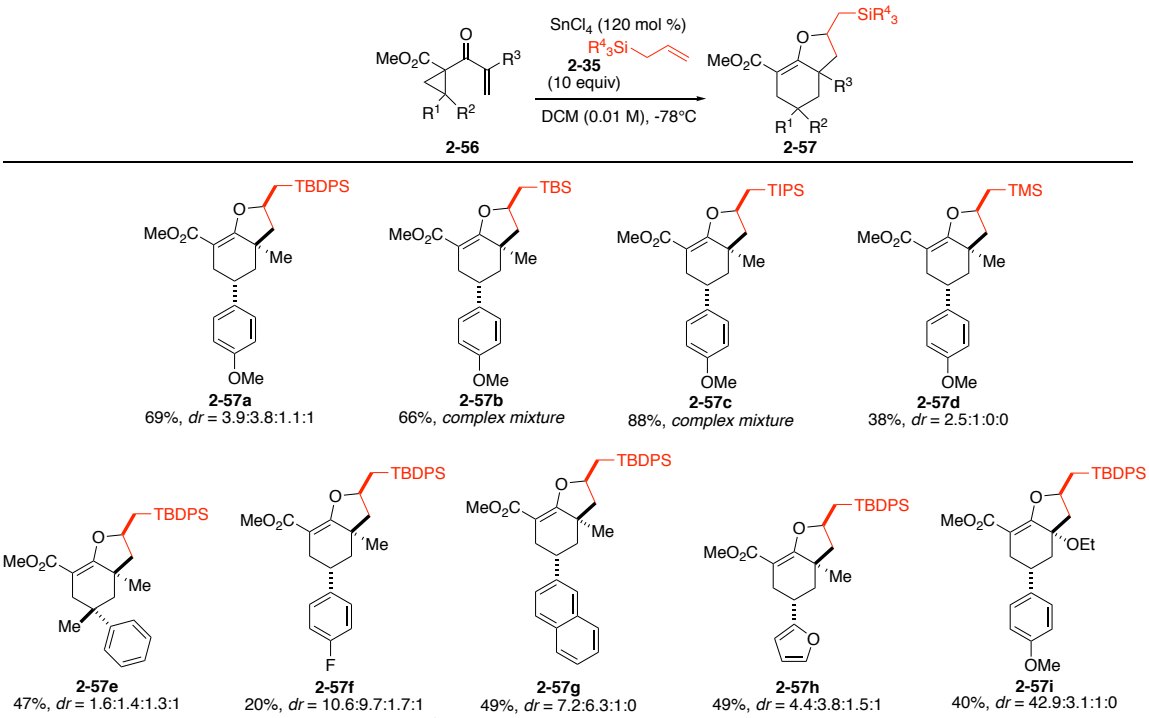
Entry	Loading (mol %)	Conc. (M)	Time (hr)	Yield (%)[a]
1	20	0.1	3	20
2	20	0.05	1	33
3	20	0.01	2	37
4	50	0.01	1	49
5	100	0.01	0.25	48
6	**120**	**0.01**	**1**	**69**

[a] Isolated yields after column chromatography.
[b] FHN products were not isolated.

2.5.2 *Substrate Scope and Limitations*

With optimized conditions in hand, substrate scope was then examined (Scheme 2.18). A number of cyclopropane donors proved viable toward this formal [3+2] reactivity. Yields of products in this formal [3+2] reactivity followed similar trends to

those observed earlier in the allylative FHN cyclization. An α-ethoxy vinyl substituent also drastically improved diastereoselectivity. Bulky allylsilanes, such as allyl-TBDPS, allyl-TBS, allyl-TIPS afforded the highest yields due to drastically encumbered desilylation. Employing a labile allylsilane, such as allyl-TMS, was not tolerated due to the rapid rate of desilylation, giving only a 38% yield of the hexahydrobenzofuran product.



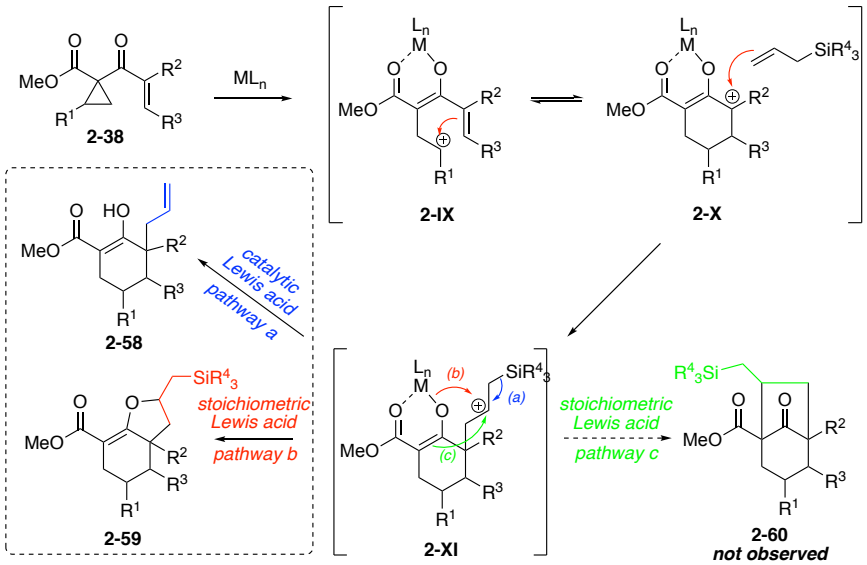
[a] Isolated yields. [b] Stereochemistry shown for the major diastereomer.

Scheme 2.18 Scope of the Tandem, Interrupted, FHN Cyclization/Formal [3+2] Cycloaddition

2.6 Mechanistic Rationale of Allylative and Formal [3+2] Interrupted FHN Products

In the preceding investigations of the FHN cyclization, only donor-acceptor-acceptor cyclopropanes were used. The mechanism (Scheme 2.19) is suspected to proceed first by activation by Lewis acid, inducing ring opening to form a stabilized,

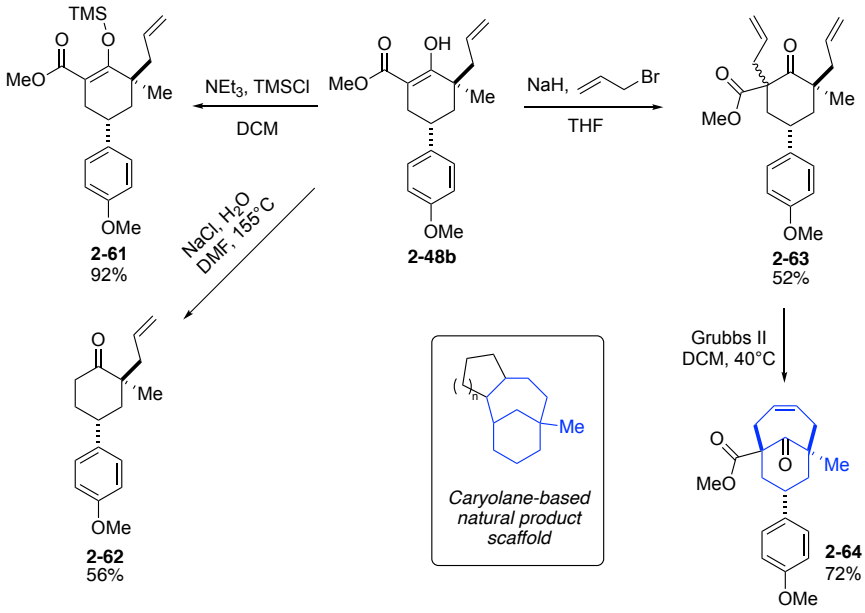
secondary acyclic cation. This acyclic intermediate then undergoes ring closing via attack by the vinyl substituent, forming a cyclic oxyallyl cation. Because of the second acceptor group, this oxyallyl cation has a localized charged in the tertiary α'-position, which undergoes olefin attack by the appropriate allylsilane. A acyclic, β-silyl stabilized cation is formed, which then undergoes one of two pathways: (a) in the catalytic Lewis acid conditions, a labile allylsilane is used, which is desilylated via Hosomi-Sakurai-type elimination to form the allylated cyclohexanone products, or (b) in the stoichiometric Lewis acid conditions, a sterically encumbered allylsilane is used (hindering desilylation), which undergoes *O*-alkylation to form the formal [3+2]-cycloaddition, hexahydrobenzofuran products. A third pathway (c) is also possible, which forms *C*-alkylated [3+2]-cycloaddition products; these products were not observed an any of our studies, likely due to the decreased nucleophilicity at the α-position owed to the secondary acceptor.



Scheme 2.19 Suspected Mechanism of Interrupted FHN Cyclizations with Allylsilanes

2.7 Potential Utility of Interrupted FHN Products

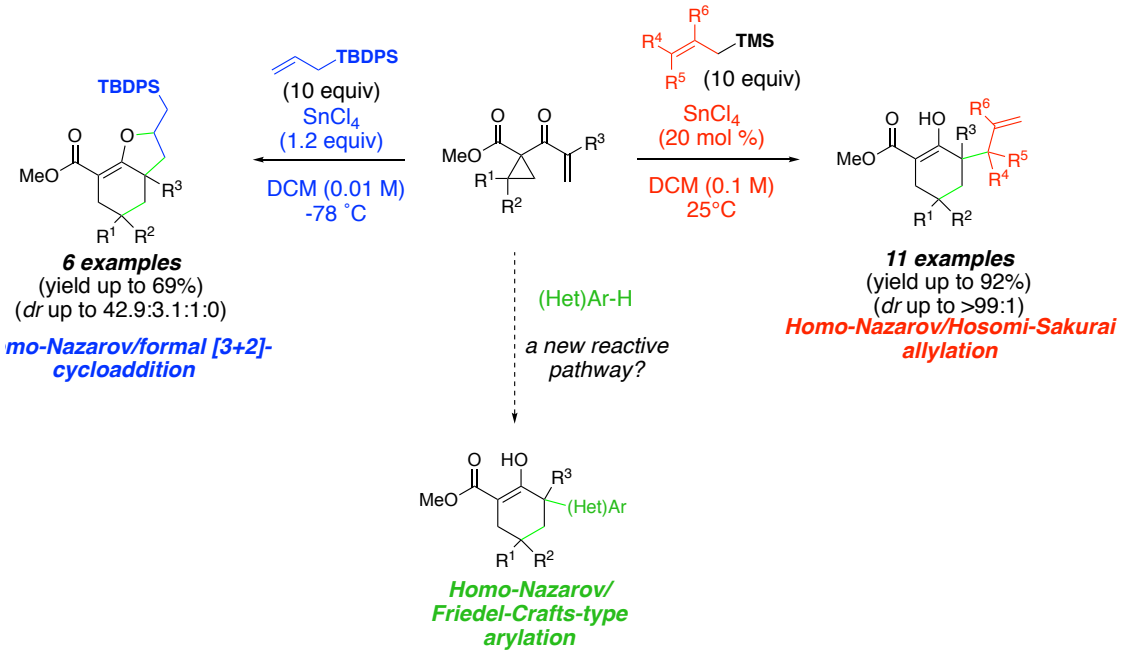
The potential synthetic utility of the products formed through the interrupted FHN reaction was demonstrated through a number of derivatizations (Scheme 2.20). Firstly, allylated cyclohexenols are easily capped with TMSCl and triethylamine, forming TMS-enol ethers that can be used in further derivatizations. This TMS capping reaction was important in elucidating diastereomeric ratios of cyclohexenol products in the allylative, interrupted, FHN cyclization. Secondly, the ester groups can be removed via Krapcho decarbalkoxylation conditions to give cyclohexanones. Finally, a second allylation followed by a Grubbs' RCM sequence leads to bicyclo[3.2.1]nonane frameworks, a scaffold found in the caryolane-type natural products. These simple derivatizations show the synthetic potential of these interrupted FHN products.



Scheme 2.20 Synthetic Derivatizations of Interrupted FHN Products

2.8 A Novel, (Hetero)Arylative, Interrupted FHN Cyclization

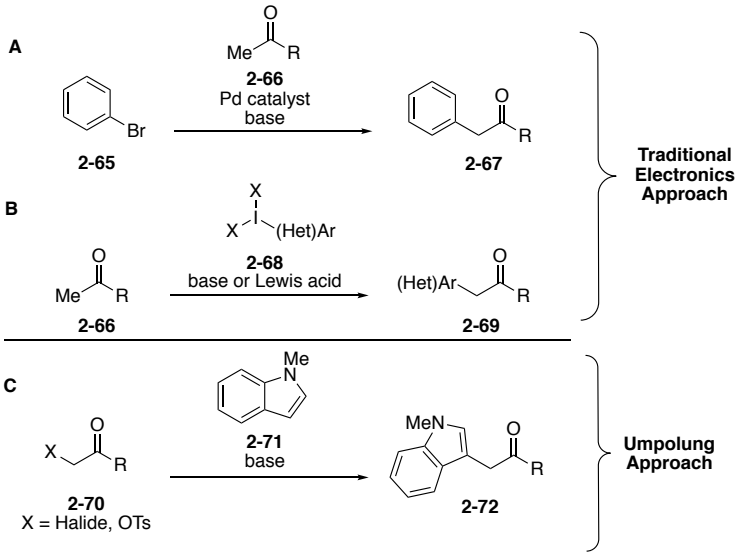
With robust conditions for both an allylative and a formal [3+2] cycloaddition interrupted FHN cyclization, it was then hypothesized that a similar, unexplored, (hetero)arylative variant could be established by similar mechanism, generating a variety of interesting α-(hetero)aryl cyclohexanones/cyclohexenols. In this pathway, the desired (hetero)aryl nucleophile would undergo Friedel-Crafts attack on the cyclic oxyallyl intermediate within the FHN mechanism. Reactivity of this type is precedented by West and coworkers, who established a Nazarov variant of this reaction.[38] In this work, donor-acceptor-acceptor cyclopropanes would be used as a means to promote catalysis and regiospecific (hetero)arylations. Henceforth, this would represent a divergent synthetic pathway in the interrupted FHN cyclization in which a simple change in nucleophile would result in drastically different products (Scheme 2.21).



Scheme 2.21 Divergent Pathways in the Interrupted FHN Cyclization

2.8.1 Project Justification

Methodologies have been developed to access α-(hetero)aryl cyclohexanones and generally fall into two different categories (Scheme 2.21). In the first category, normal polarity approaches have been developed utilize the nucleophilic nature of the α-position of carbonyls. Generally, a ketone is exposed to a base, generating an enolate, which subsequently attacks the electrophilic position of a (hetero)arene. In many examples, palladium catalysts are used to mediate such processes, readily providing access to α-(hetero)aryl ketones (Scheme 2.22A).[47] In other examples, either base or Lewis acid is use to generate an enolate and hypervalent iodide reagents act as electrophilic centers for α-(hetero)arylation (Scheme 2.22B).[48] In a more recent example, MacMillan and co-workers showcased an umpolung approach toward α-(hetero)aryl ketones using a base-mediated generation of oxyallyl cations from α-tosyloxyketones (Scheme 2.22C).[49] A (hetero)arylative, interrupted FHN cyclization would represent another complementary umpolung approach toward α-(hetero)aryl cyclohexanones.



Scheme 2.22 Previous Approaches Toward α-(Hetero)Aryl Ketones

This methodology would also provide access to a number of biologically relevant natural products containing this α-(hetero)aryl cyclohexanone structural motif (Figure 2.1). Some examples include walsucochinoid D,[50] an 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor, which could play a role in regulating type 2 diabetes, and the antibacterial diterpenoid natural product, 1-oxofurruginol.[51] Other intriguing α-(hetero)aryl natural products have also been isolated, including the antiviral alkaloid tubingensin A[52] and the anticancer natural product fevicordin A.[53]

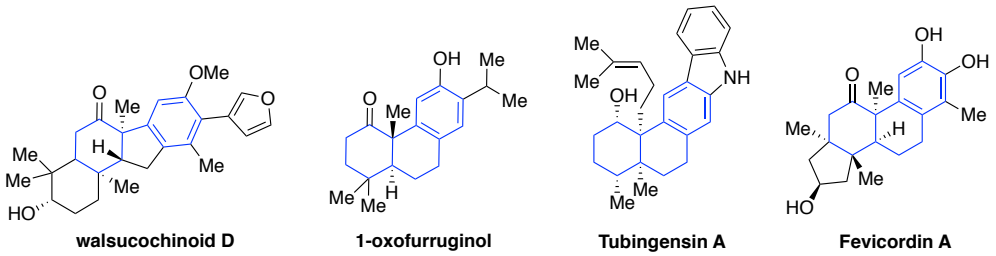
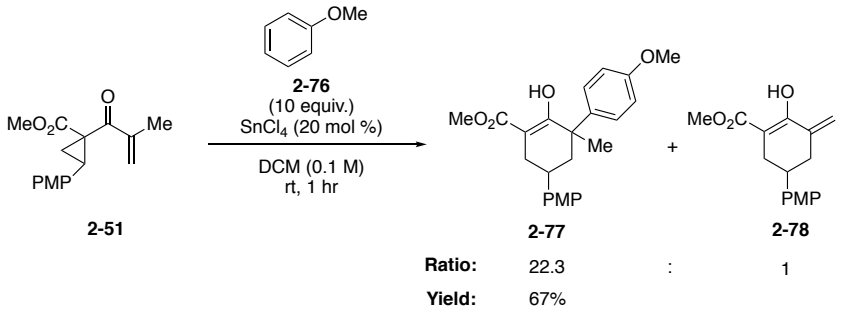


Figure 2.1 α-(Hetero)Aryl Cyclohexanone Natural Products

2.8.2 Reaction Design and Proof of Concept

Due to its effectiveness in the previous allylative and formal [3+2] interrupted FHN cyclization, the PMP cyclopropane donor was again chosen as a model substrate. Anisole was chosen as the nucleophile for two reasons: (1) anisole has been shown as an effective nucleophile in a number of previous Friedel-Crafts transformations, and (2) *para* regioselectivity has been demonstrated for previous Friedel-Crafts reactions with anisole. The study began utilizing the optimized conditions from the previous allylative study (20 mol % $SnCl_4$, 0.1 M in DCM, and 10 equivalents of nucleophile) to effect the transformation (Scheme 2.23). Gratifyingly, the reaction proceeded smoothly, giving the desired α-PMP cyclohexanone in 67% yield as a keto-enol mixture. The reaction was also very chemoselective, producing a 22.3:1 ratio of the desired aryl-trapped product to the

FHN product. The represented the first literature example of an arylative, interrupted FHN cyclization.



Scheme 2.23 Initial Arylative Interrupted FHN Cyclization Reaction

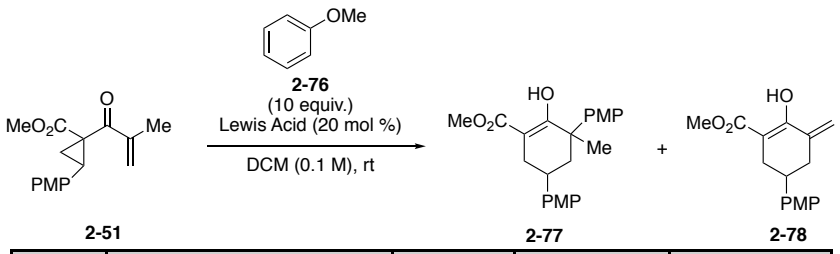
2.8.3 Reaction Optimization

After obtaining this pleasing initial result, a number of efforts were made to further optimize the reaction, focusing on increasing yield of and selectivity toward the arylated product, decreasing catalyst loading, and finding a suitable alternative catalyst to the highly toxic $SnCl_4$. A number of 2+, 3+, and 4+ Lewis acids were screened (Table 2.7). Unfortunately, no suitable alternative to $SnCl_4$ was found, producing the highest yields and selectivity toward the desired product. However, $InCl_3$ gave comparable yields to $SnCl_4$ but approximately half of the selectivity.

Considering the high yields of each catalyst, both were taken forward for further loading studies (Table 2.8). Reducing the loading of $SnCl_4$ to 10 and 5 mol % decreased yield to 56% and 50% respectively. Similarly, decreasing the loading of $InCl_3$ to 15, 10, and 5 mol % also reduced yield to 65%, 62%, and 38% respectively. With only a decrease of 7% in yield, 10 mol % $InCl_3$ would be taken forward as a suitable, non-toxic back-up catalyst for substrates not compatible with $SnCl_4$. All other attempts to optimize the reaction, including altering concentration, anisole loading, solvent, and temperature

led to no improvement. The optimal conditions moving forward were 20 mol % $SnCl_4$ (with 10 mol % $InCl_3$ as a back-up), 10 equivalents of the (hetero)arene, and the cyclopropane at 0.1 M in DCM reacting at room temperature.

Table 2.7 Lewis Acid Screen

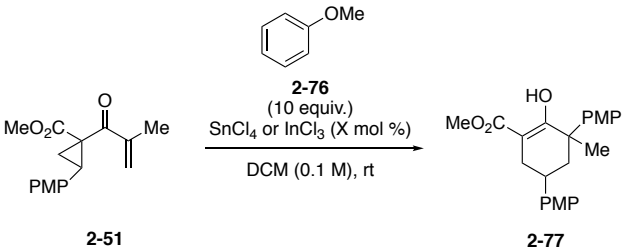


2-51 2-77 2-78

Entry	Lewis acid	Time (hr)	Yield (%)[a] 2-77	Yield (%)[a] 2-77
1	**$SnCl_4$**	**1**	**67**	**3**
2	$Mg(OTf)_3$	27	63[b]	11
3	$Cu(OTf)_3$	1.5	0	25
4	$Al(OTf)_3$	1	0	26
5	$In(OTf)_3$	1	11	19
6	$Sc(OTf)_3$	1	10	15
7	$Ga(OTf)_3$	1	0	24
8	$Ni(OTf)_2$	21	40[b]	15
9	$La(OTf)_3$	21	40[b]	16
10	$Zn(OTf)_2$	1.5	0	26
11	$Yb(OTf)_3$	1	0	0
12	$In(OTf)_3$ + LiCl (1 eq.)	1	19	26
13	$BF_3 \bullet Et_2O$	1	0	0
14	**$InCl_3$**	**24**	**69**	**6**
15	$TiCl_4$	24	0	0
16	$Ca(NTf)_2 \bullet n\text{-}Bu_4NPF_6$	0.5	0	36

[a] Isolated yields after column chromatography.
[b] Product yields skewed due to significant impurities.

Table 2.8 Optimization of Catalyst Loading



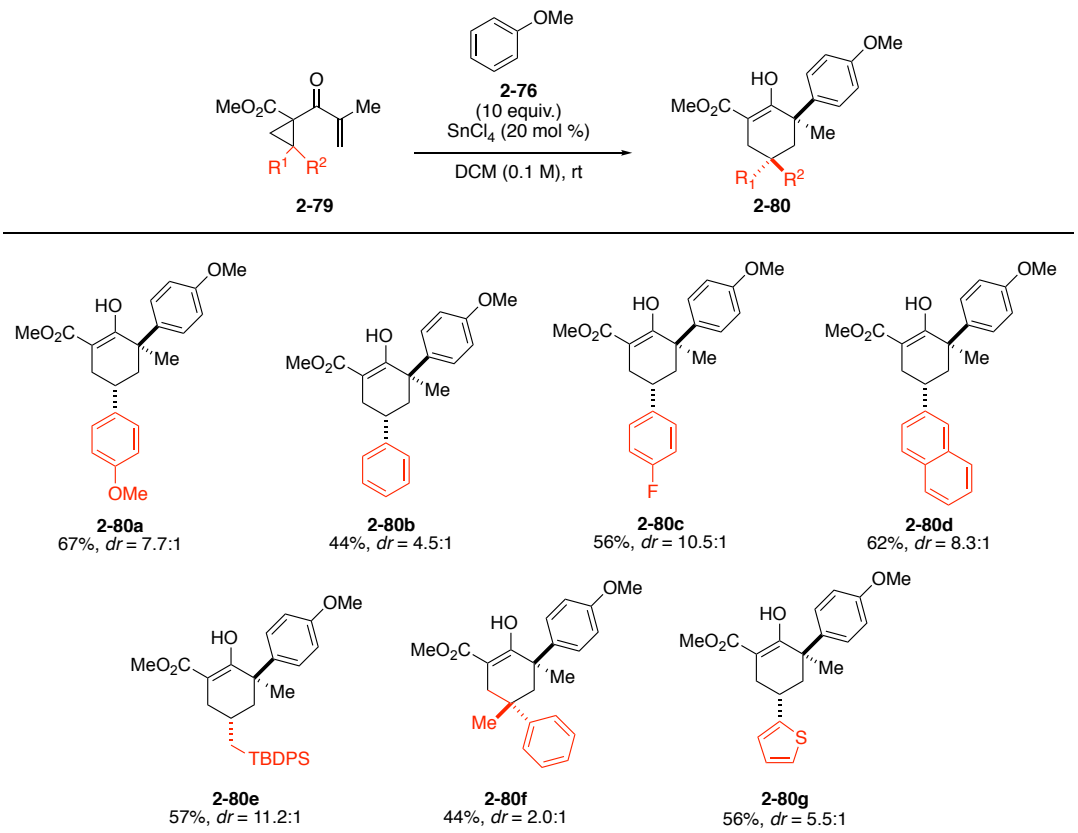
2-51 2-77

Entry	Lewis acid	Loading (mol %)	Time (hr)	Yield (%)[a]
1	**$SnCl_4$**	**20**	**1**	**67**
2	$SnCl_4$	10	1	56
3	$SnCl_4$	5	1	50
4	$InCl_3$	20	24	69
5	$InCl_3$	15	24	65
6	**$InCl_3$**	**10**	**24**	**62**
7	$InCl_3$	5	24	38

[a] Isolated yields after column chromatography.

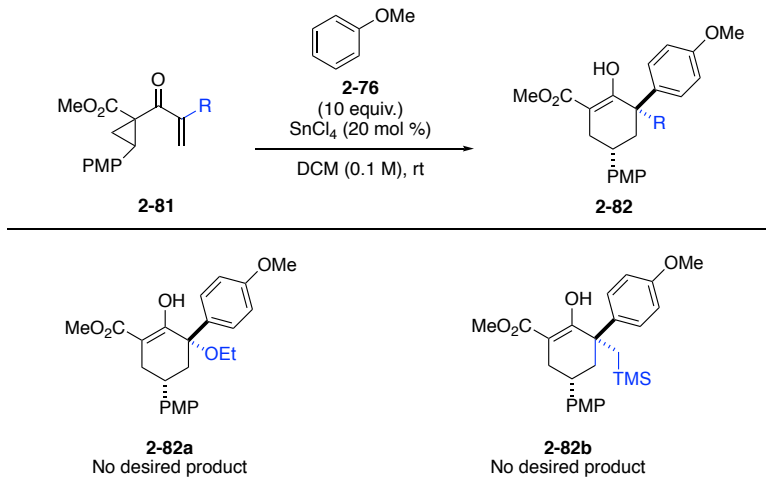
2.8.4 Reaction Scope

After obtaining the optimized conditions, substrate scope was examined. First, a number of different donor groups on the cyclopropane were tested using anisole as the nucleophilic trapping agent (Scheme 2.24). More electron deficient donors (Ph, 4-F-Ph) were well tolerated, providing products in moderate yields (44% and 56%, respectively). A β-silyl stabilized cation provided the aryl-trapped product in 57% yield with good diastereoselectivity, likely attributed to a steric effect of TBDPS. A tertiary cation (R^1 = Me, R^2 = Ph) was also a useful substrate, but provided low diastereoselectivity (2.0:1). Finally, a heteroaromatic donor was well suited for reactivity, giving the desired product in 56% yield.



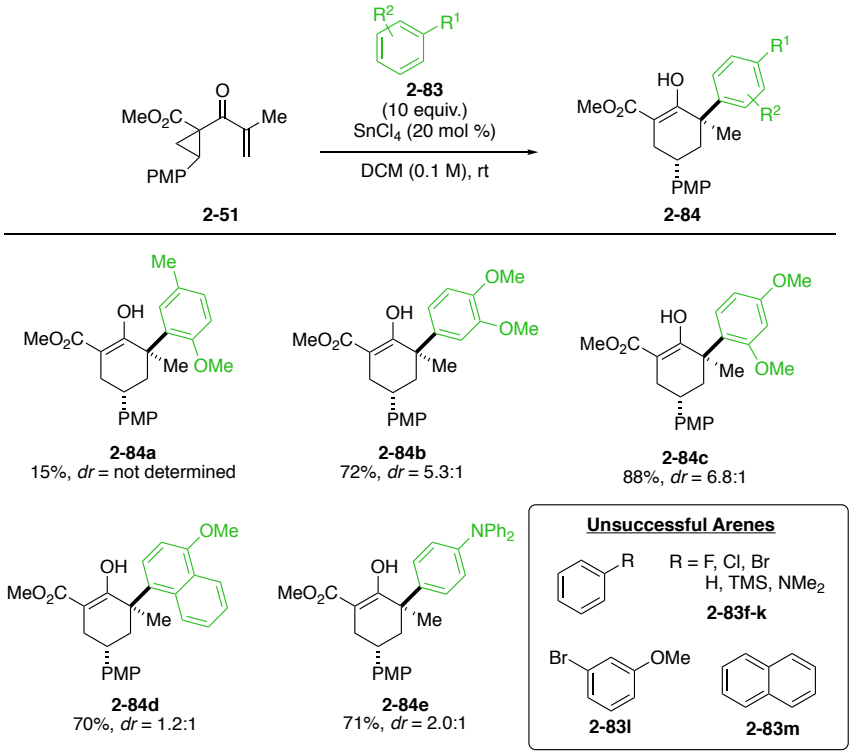
Scheme 2.24 Examination of Cyclopropane Donors

Next, two vinylic substituents other than methyl were examined (Scheme 2.25). When methyl is replaced with an ether substituent, no desired product is obtained, likely due to the reduced electrophilicity of the oxyallyl cationic intermediate. This is in stark contrast to the result obtained in the allylative interrupted FHN study, which gave good yields and a single diastereomer. Adding a β-silyl substituent also resulted in no desired product; only FHN product was obtained. This is likely attributed to the quick Hosomi-Sakurai-type elimination of the silyl group.



Scheme 2.25 Investigation of Vinylic Substituents

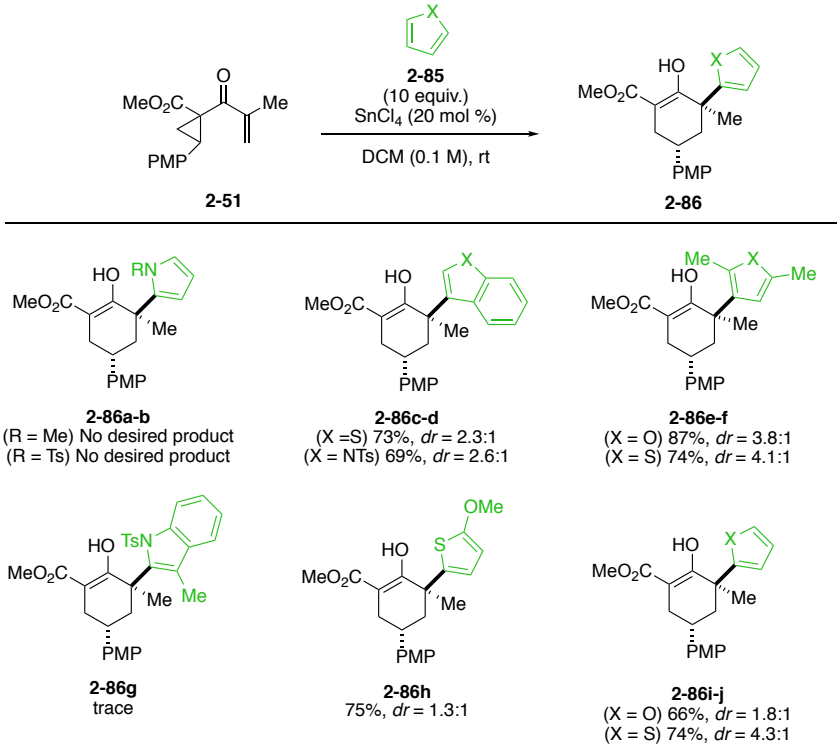
Thirdly, a set of arene nucleophiles besides anisole was investigated (Scheme 2.26). Blocking the 4-position of anisole with a methyl group (thus inducing attack at the 2-position) drastically reduces yield, indicating a significant steric effect preventing aryl attack at the 2-position. Both 1,2- and 1,3-dimethoxybenzene served as effective nucleophiles giving the desired product in 72% and 88% yields respectively. 1-methoxynaphthalene was also a competent nucleophile, giving the 4-substituted 1-methoxynaphthalene product exclusively in 70% yield. A non-basic aniline derivative, triphenylamine, was effective as well; however a basic aniline derivative, such as *N,N*-dimethylaniline, was not efficacious, likely due to catalyst poisoning by the basic amine. Several electron deficient arenes (**2-83,f-m**) were examined as well. However, no desired products were obtained, which can be attributed to their reduced nucleophilicity.



Scheme 2.26 Investigation of Various Arene Nucleophiles

Finally, a number of heteroarenes were investigated as effective trapping agents (Scheme 2.27). *N*-methyl and *N*-tosyl pyrroles gave no desired products; *N*-methyl pyrrole was too effective a nucleophile, and attacked the acyclic cation produced upon ring opening. *N*-tosyl pyrrole, on the other hand, is not as nucleophilic; only FHN product was obtained. Benzothiophene and *N*-tosyl indole were effective nucleophiles, giving the desired products in 73% and 69% yield respectively. 2,5-dimethylfuran and 2,5-dimethyl thiophene also worked well, showing that steric influence has little effect on smaller heteroarenes nucleophiles. Furan and thiophene were efficacious, giving only 2-substituted products, due to the increased nucleophilicity at that position. However, N-tosyl-3-methylindole was not a potent nucleophile for this transformation, likely due to significant steric influence between the tosyl and methyl substituents. The electron-rich

2-methoxythiophene proceeded to give exclusively the 5-substituted product in 75% yield.



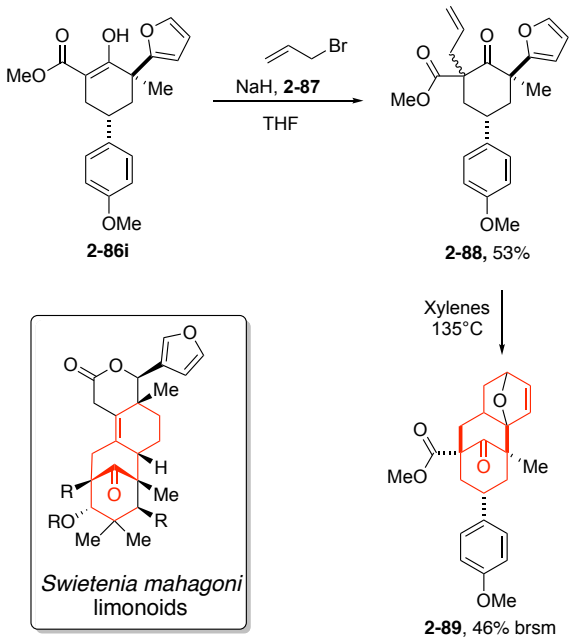
Scheme 2.27 Investigation of Heteroarene Nucleophiles

All products contained in the above substrate scope were obtained as highly complex keto-enol tautomers and diastereomeric mixtures. As such, two methods were examined to simplify NMR spectra to definitively obtain *dr*. The first method, *O*-silylation with TMSCl, was not effective likely due to the significantly sterically encumbered enol. However, subjecting each substrate to Krapcho decarbalkoxylation conditions provided greatly simplified NMR spectra, allowed for definitive *dr* determinations via crude NMR of the Krapcho reaction, and provided effective separation of the diastereomers in column chromatography. NOE NMR of the minor diastereomers revealed a correlation between the benzylic proton and the α-methyl groups that was not observed in the major diastereomers. This provided evidence that (hetero)arene

substituents have a *trans*- relationship across the cyclohexanone. This also gave evidence to nucleophiles favoring oxyallyl approach opposite the aryl donor in order to minimize unfavorable 1,3-diaxial interactions.

2.8.5 Utility of α-(Hetero)Aryl Cyclohexanone Products

The potential synthetic utility of the products generated from the arylative interrupted FHN cyclization was demonstrated through a simple derivatization sequence (Scheme 2.28). Inspired by Padwa's work on alkenes tethered to furans,[54] it seemed sensible to attempt to tether an allyl group to the α-furyl substituted cyclohexanones generated from the demonstrated arylative interrupted FHN cyclization. Cyclohexanone **2-86i** was allylated using sodium hydride and allyl bromide to form the now tethered alkene system **2-88** in 53% yield as an inseparable diastereomeric mixture of 7.1:3.6:3.1:1 *dr*. This mixture was then heated to promote a Diels-Alder [4+2]-cycloaddition to form the tricyclic core **2-89** in 46% yield (based on recovered starting material), a scaffold found in the *Swietenia mahagoni* limonoid natural products.[55]

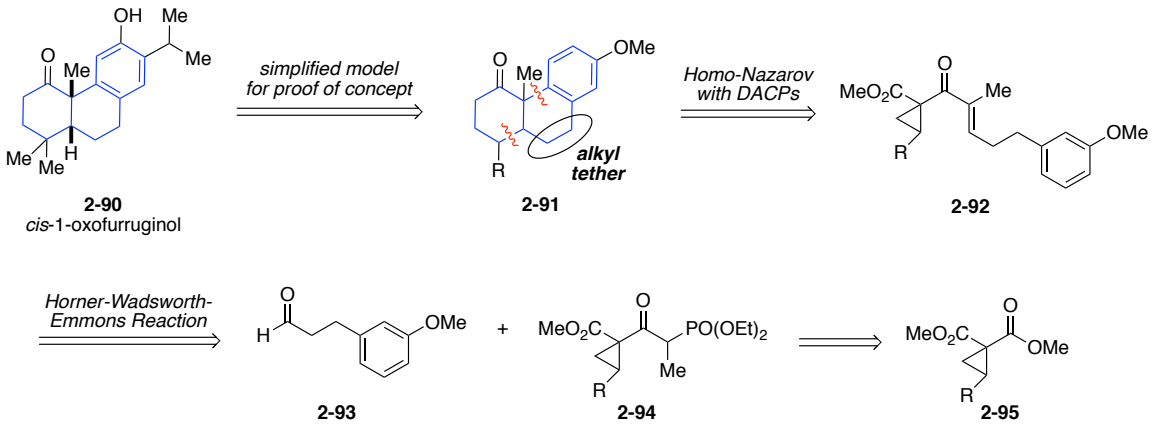


Scheme 2.28 Synthetic Utility of Arylative Interrupted FHN Products

2.9 Efforts Toward an Intramolecular Arylative Interrupted FHN Cyclization

Considering each of the examples thus far of an interrupted FHN cyclization (allylative, alkylative, or arylative) has been an intermolecular transformation, one might acknowledge the need for an intramolecular variant. As shown previously in Figure 2.1, many α-(hetero)aryl cyclohexanone natural products have (hetero)aryl substituents linked directly to the cyclohexanone core directly at the α-position and at the β-position through an alkyl tether. As such, a simple alkyl tether to the (hetero)aryl nucleophile in the interrupted FHN cyclization would provide facile access to this polycyclic architecture found in these natural products (Scheme 2.29). Using *cis*-1-oxofurruginol as an example, one might envision arriving at the polycyclic framework using an intramolecular, arylative, interrupted FHN cyclization. The *cis*-framework in this strategy is essential, as it is expected that the tethered aryl nucleophile will attack from the same side from which it is tethered. The aryl nucleophile would be anchored to the vinyl group via an ethylene

tether. This ethylene tether would be attached via a Horner-Wadsworth-Emmons reaction between the aldehyde **2-93** and the β-ketophosphonate ester **2-94**. **2-94** could be accessed via a deprotonated phosphonate and the cyclopropyl diester **2-95**.

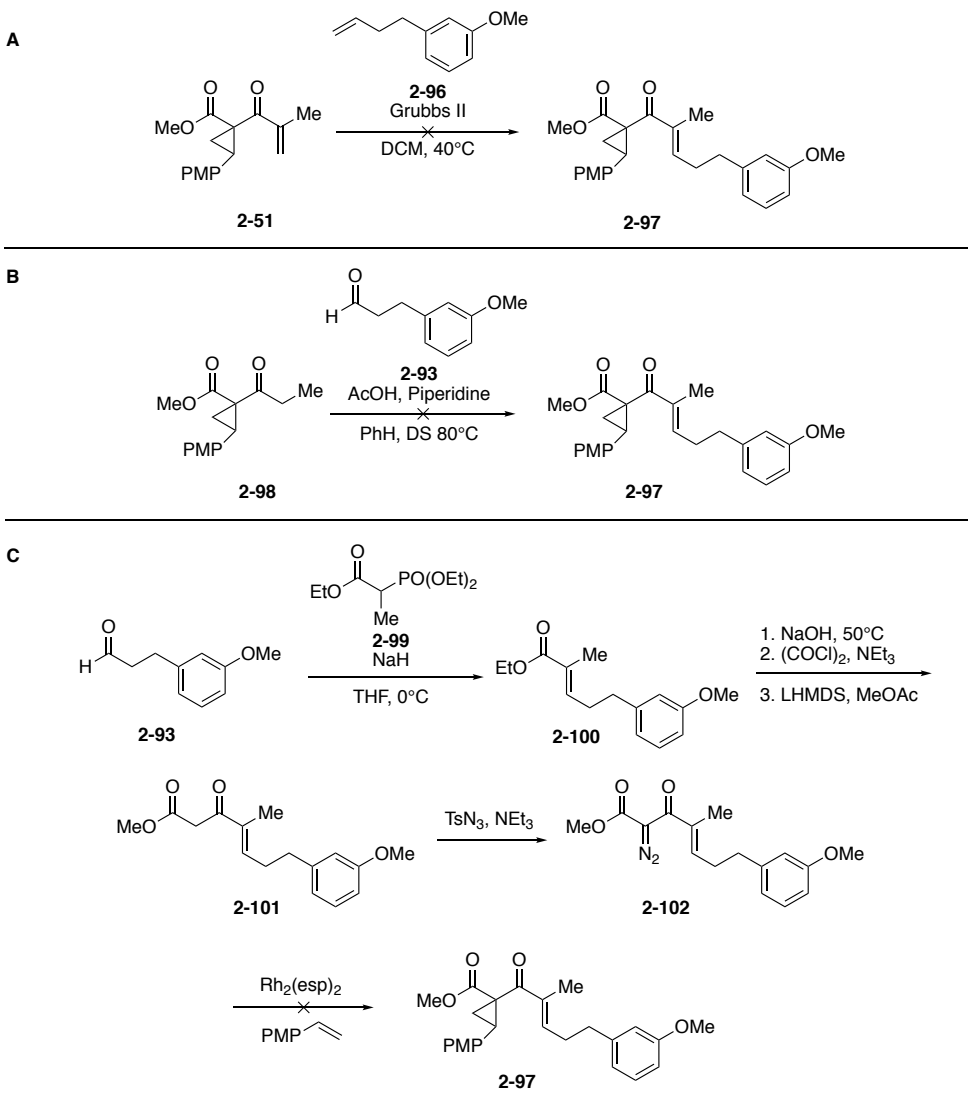


Scheme 2.29 Retrosynthetic Analysis Toward an Intramolecular, Arylative, Interrupted FHN Cyclization

2.9.1 Previous Efforts

Sometime before the above synthetic route was proposed, Raynold Shenje proposed and attempted a number of sequences toward the tethered arene substrate. His attempted routes are summarized in Scheme 2.30. His first synthetic attempt (Scheme 2.30A) involved a Grubbs cross metathesis of a substrate from the previous interrupted FHN studies with a homoallylic 3-methoxybenzene, with no success. In this pathway, there was likely dimerization with the alkene **2-96**. Secondly, Shenje attempted a Knoevenagel condensation of the β-ketoester cyclopropane **2-98** with aldehyde **2-93**, again with no success (Scheme 2.30B). In this attempt, the high temperatures likely caused ring-opening degradation products originating from the cyclopropane. His final synthetic attempt involved tethering the arene to an unsaturated ester first, then building the donor-acceptor-acceptor cyclopropane, again, with no success (Scheme 2.30C). In this route, as part of the final cyclopropanation, the unsaturated ketone provides another

alkene center that can react and form a cyclopropyl dimer product. The route proposed in the above retrosynthetic analysis provides a number of advantages over previous attempts: (1) assembling the cyclopropane first prevents dimerization issues with cyclopropanations in the prescence of two alkenes, (2) all subsequent reactions after cyclopropanation are conducted at low temperature, slowing ring-opening degradation reactions of cyclopropanes at higher temperatures, and (3) attaching the tethered arene in the final step is much more modular, allowing for rapid generation of other strategic analogs.



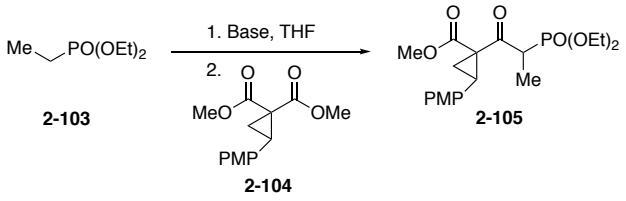
Scheme 2.30 Raynold Shenje's Previous Attempts at a Tethered Aryl Nucleophile

2.9.2 Current Work and Proof of Concept

This work began with deprotonation of the commercially available diethyl ethylphosphonate (**2-103**) and reacting with the cyclopropane **2-104**, a common intermediate in the previous interrupted FHN studies, to produce the β-ketophosphonate cyclopropane **2-105**. After several optimizations (Table 2.9), yields for this carbonyl addition were increased from 42% to 82% yield by using 1.2 equivalents of deprotonated phosphonate **2-103** to 1 equivalent of cyclopropane **2-104**. Following this, the Horner-

Wadsworth-Emmons reaction with aldehyde **2-93** proved to be much more difficult than anticipated, giving an initial yield of 12%. After a host of optimizations (Table 2.10), including altering bases and equivalents of bases, yield was increased to only 39%. However, enough material was obtained to continue forward to probe the viability of the intramolecular, arylative, interrupted FHN cyclization. Gratifyingly, upon initial exposure to the optimized conditions of the allylative and arylative interrupted FHN studies (excluding the arene nucleophile), the desired product was obtained in 21% yield. Changing Lewis acid catalyst to $In(OTf)_3$, however, increased yield to 41%. To our knowledge, this represented the first example and proof of concept toward an intramolecular, arylative, interrupted FHN cyclization (Scheme 2.31). This also provides an important stepping-stone toward using these interrupted FHN methodologies in the synthesis of polycyclic α-arylcyclohexanone natural products scaffolds.

Table 2.9 Optimization of Phosphonate Addition

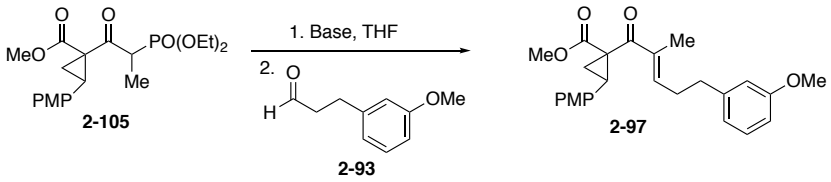


2-103 **2-104** **2-105**

2-103 (equiv.)	2-104 (equiv.)	Base (equiv.)	Yield (%) 2-105
1	3	*n*-BuLi (1.1)	42
1.2	1	*n*-BuLi (1.3)	63
1	1.2	*n*-BuLi (1.1)	53
1.2	1	LiHMDS (1.3)	0
1.2	1	*n*-BuLi	82[b]

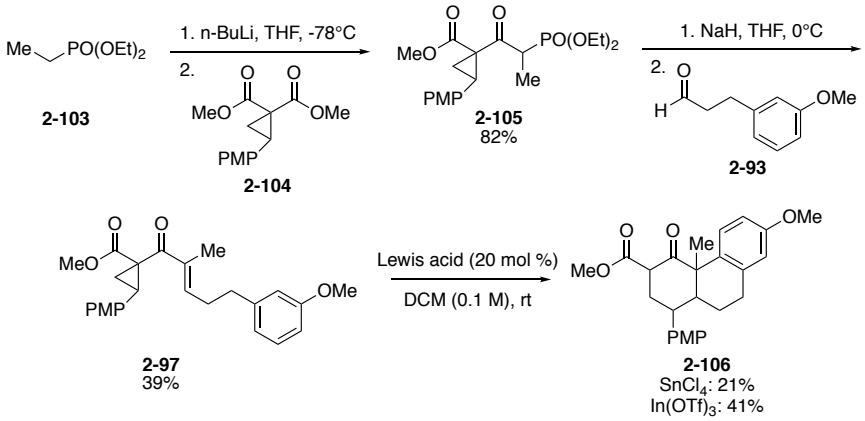
[a] Isolated yields. [b] 1.5g scale

Table 2.10 Optimization of Horner-Wadsworth-Emmons Reaction



2-105 (equiv.)	2-93 (equiv.)	Base (equiv.)	Yield (%) 2-97
1.1	1	NaH (1.3)	12
1.1	1	NaH (1.2)	26[b]
1.1	1	*n*-BuLi (1.15)	6
1.1	1	LiHMDS (1.2)	10
1.1	1	NaH (5)	9[c]
1.1	1	NaH (1.2)	18[d]
1.1	1	NaHMDS (1.2)	9
1.1	1	DBU (1.2)	10[e]
1.1	**1**	**NaH (1.2)**	**39[d,f]**

[a] Isolated yields. [b] Fresh NaH used.
[c] Stirred while warming to room temperature overnight.
[d] Slow addition of aldehyde over three hours.
[e] Stirred at room temperature overnight.
[f] Stirred with warming to room temperature overnight.

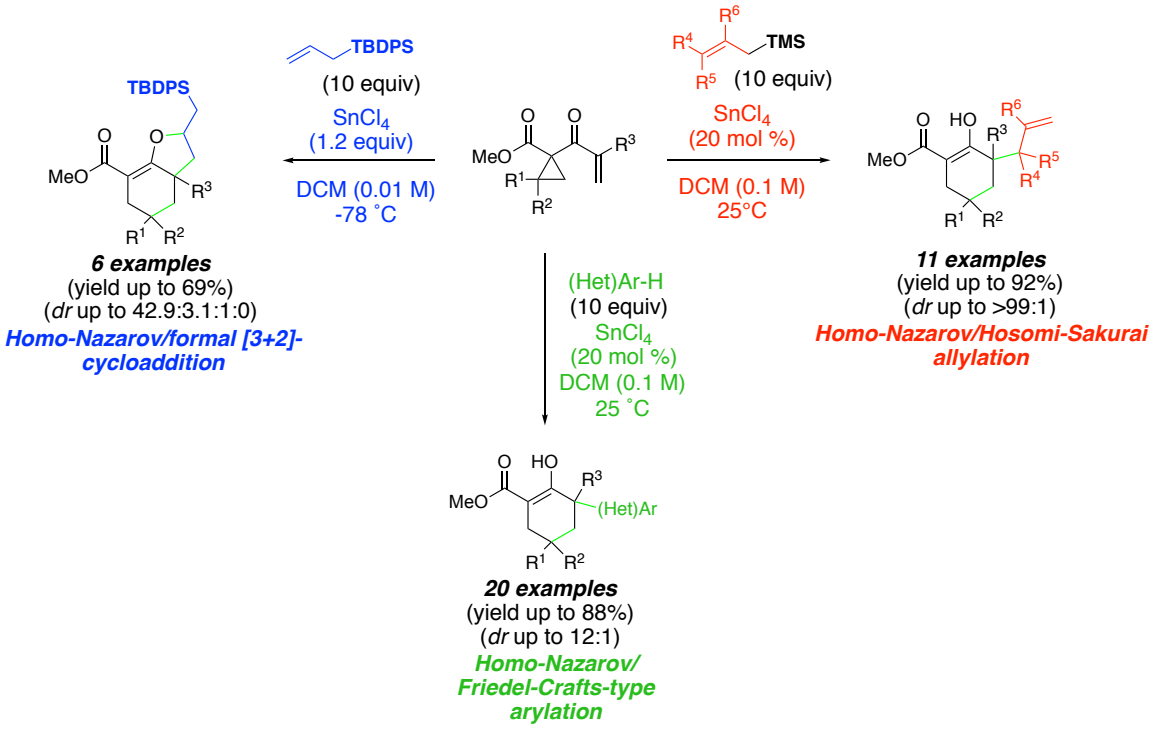


Scheme 2.31 Current Synthetic Route Toward α-Arylcyclohexanone Scaffolds

2.10 Summary: Allylative, Alkylative, and Arylative Methods in the Interrupted FHN Cyclization

FHN methodologies are becoming more prevalent in the literature toward the constructive of highly complex cyclohexanone scaffolds; however, until the publication of this work, only one known publication of an interrupted variant was known. Included in this chapter are the first Lewis acid-catalyzed allylative and arylative interrupted FHN cyclizations, and a stoichiometric Lewis acid-mediated alkylative interrupted FHN cyclization. The interruption of the FHN reaction originates from the ability of competent nucleophiles to capture cyclic oxyallyl cationic intermediates within the FHN mechanism.

The first catalytic allylative method was disclosed using 20 mol % $SnCl_4$ and allylsilane nucleophiles as nucleophiles toward a FHN ring-opening/ring-closing/Hosomi-Sakurai cascade. Reaction products were provided in moderate to high yields and moderate to excellent diastereoselectivities. Concurrently, an alkylative method was disclosed using stoichiometric $SnCl_4$ and allylsilanes to initiate a FHN/formal [3+2]-cycloaddition cascade toward the formation of unique hexahydrobenzofuran scaffolds. In a follow-up study, it was also discovered that (hetero)arenes are effective nucleophiles toward interrupting the FHN cyclization through a Friedel-Crafts alkylation pathway to form α-(hetero)aryl cyclohexanones using $SnCl_4$ as a Lewis acid catalyst. Follow-up studies toward intramolecular, arylative, interrupted FHN cyclizations have also began. These studies serve as some of the pioneering literature in catalytic, allylative, alkylative, and arylative interrupted FHN cyclization methodologies.



Scheme 2.32 Scope of the Interrupted FHN Reaction Thus Far

2.11 Experimental Section

2.11.1 Interrupted FHN Cyclizations with Allylsilanes

For both experimentals and NMR spectra for work in the interrupted FHN cyclization using allylsilanes, see Shenje, R.; Williams, C. W.; Francois, K. M.; France, S. Catalysis and Chemodivergence in the Interrupted, Formal Homo-Nazarov Cyclization Using Allylsilanes. *Org. Lett.* **2014,** *16* (24), 6468-6471.

2.11.2 Intermolecular, (Hetero)Arylative, Interrupted FHN Cyclizations

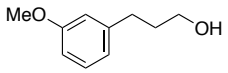
For both experimentals and NMR spectra for work in the intermolecular, (hetero)arylative interrupted FHN cyclization, see Williams, C. W.; Shenje, R.; France, S. Catalytic, Interrupted Formal Homo-Nazarov Cyclization with (Hetero)arenes: Access to

α-(Hetero)aryl Cyclohexanones. *J. Org. Chem.* **2016**, *81*, 8253-8267.

2.11.3 Intramolecular, Arylative, Interrupted FHN Cyclizations

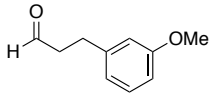
Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-65μm) or preparative thin-layer chromatography (prep-TLC) using Silicycle silica gel F_{254} (1000 μm) plates and solvents indicated as eluent with nitrogen for pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light.

Infrared (IR) spectra were obtained using a Shimadzu IRAffinity-1S FTIR with a Specac Quest ATR attachment. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, or Bruker 400 MHz and 500 MHz spectrometers with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer using $PhCF_3$ as an external standard. ^{1}H and ^{19}F NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Mass spectra were obtained using a MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of 10,000 using PFK (perfluorokerosene) as an internal calibrant. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).



SI2-1

3-(3-methoxyphenyl)propan-1-ol: Lithium aluminum hydride (4.21 g, 111 mmol) was added to a flask, suspended in THF (70 mL), and cooled to 0°C. 3-(3-methoxyphenyl)propanoic acid (5.00 g, 27.7 mmol) in THF (70 mL) was added slowly and stirred at 0°C for 2 hours. The reaction was quenched at 0°C with sat. aq. NH_4Cl until evolution of H_2 ceased and EtOAc was added. 1 M HCl was then added until the resulting aluminum salts dissolved. The resulting mixture was extracted three times with EtOAc, washed with sat. aq. $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated to give the resulting alcohol (4.6702 g, >99%) as a brown oil. The alcohol was carried forward without further purification. Characterization was consistent with that previously reported.[56]

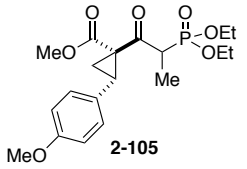


2-93

3-(3-methoxyphenyl)propanal: IBX (3.30 g, 11.7 mmol) was added to a flask and suspended in MeCN (36 mL). 3-(3-methoxyphenyl)propan-1-ol (1.52 g, 9.14 mmol) was then added neat and the mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and filtered through a pad of celite, which was rinsed with EtOAc, and concentrated to give a brown oil (1.51 g, 98% yield) which was used without further purification. Characterization was consistent with that previously reported.[57]

General procedure for phosphonate substitution on cyclopropyl diesters:

Adapted from Lee's published procedure.[58] The appropriate phosphonate (1.2 eq.) was added to a flask and dissolved in THF (1.0 M in relation to phosphonate) and cooled to -78°C. n-Butyllithium (1.3 eq.) was added and stirred at -78°C for 3 hours. The cyclopropyl diester (1.0 eq.) was dissolved in THF (1.0 M in relation to the cyclopropyl diester) and added and stirred at -78°C until the cyclopropyl diester was fully consumed by TLC analysis. The reaction was quenched with sat. aq. NH_4Cl (unless otherwise indicated), extracted three times with EtOAc, washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography.



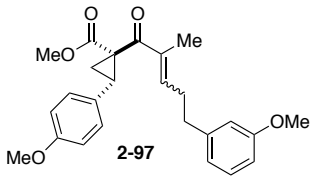
2-105

Methyl 1-(2-(diethoxyphosphoryl)propanoyl)-2-(4-methoxyphenyl)cyclopropane-1-carboxylate: Synthesized according to the general procedure using diethyl ethyl phosphonate (1.10 mL, 6.811 mmol), *n*-butyllithium (3.00 mL, 7.50 mmol), and dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate[59] (1.50 g, 5.68 mmol) for 1 hour after addition of the cyclopropyl diester. After work-up and purification (R_f = 0.14, 50% EtOAc/Hexane), the desired cyclopropyl phosphonate **2-105** (1.87 g, 82% yield) was given as a colorless oil. *Diastereomeric ratio = 4.20:3.88:1:0.* **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.36 - 7.35 (m, 0.49 H), 7.25 - 7.21 (m, 0.47 H), 7.13 - 7.09 (m, 2.06 H), 6.89 - 6.87 (m, 0.53 H), 6.82 - 6.77 (m, 2.52 H), 4.48 - 4.31 (m, 1.59 H), 4.23 - 3.98 (m, 6.85 H), 3.80 (s, 0.81 H), 3.78 - 3.76 (m, 3.54 H), 3.71 (s, 0.73 H), 3.41 (t, *J* = 8.7 Hz, 1.07 H), 3.36 (s, 0.54 H), 3.31 (s, 3.00 H), 3.16 (t, *J* = 8.9 Hz, 0.25 H), 2.94 - 2.87 (m, 0.30 H),

2.37 (dd, J = 4.6, 8.2 Hz, 1.05 H), 2.21(dd, J = 4.6, 8.5 Hz, 0.21 H), 2.09 (m, J = 4.6, 9.5 Hz, 0.21 H), 1.75 (dd, J = 4.6, 9.2 Hz, 1.19 H), 1.47 - 1.38 (m, 4.71 H), 1.36 - 1.28 (m, 8.53 H), 1.26 - 1.18 (m, 1.90 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 200.3, 168.8, 158.9, 130.3, 130.1, 127.4, 126.6, 113.8, 113.4, 113.3, 62.7, 62.6, 62.5, 62.5, 55.3, 55.2, 51.7, 51.0, 44.8, 44.3, 43.3, 36.5, 23.8, 16.4, 16.4, 16.4, 16.3, 16.3, 10.9, 10.8. **IR:** 2984 (w), 2945 (w), 1717 (m), 1697 (m), 1637 (m), 1612 (m), 1516 (s), 1246 (s), 1016 (s) cm^{-1}. **HRMS (EI)** m/z: $[M]^+$ Calcd. for $C_{19}H_{27}O_7P$ 398.1494; Found 398.1490.

General procedure for the synthesis of cyclopropyl vinyl ketones:

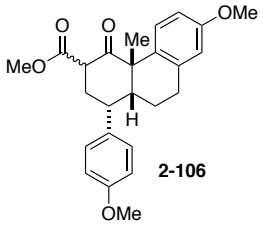
Sodium hydride (60% dispersion in mineral oil, 1.2 eq.) was suspended in THF (0.5 M in relation to NaH) and cooled to 0°C. The appropriate cyclopropyl phosphonate (1.1 eq.) in THF (0.33 M in relation to the cyclopropyl phosphonate) was added and stirred at 0°C for 30 minutes. The subsequent aldehyde (1.0 eq.) was dissolved in THF (10 mL) and added via syringe pump over 3 hours. The reaction solution was allowed to warm to room temperature overnight or until consumption of the cyclopropyl phosphonate. The reaction was then quenched with sat. aq. NH_4Cl, extracted three times with EtOAc, washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography.



2-97

Methyl (*E*)-2-(4-methoxyphenyl)-1-(5-(3-methoxyphenyl)-2-methylpent-2-enoyl)cyclo-propane-1-carboxylate: Synthesized using the above general procedure

using sodium hydride (111 mg, 2.78 mmol), cyclopropyl phosphonate **2-105** (975 mg, 2.45 mmol) and 3-(3-methoxyphenyl)propanal (369 mg, 2.25 mmol) stirring at room temperature overnight. After work-up and purification (R_f = 0.46, 20% EtOAc/Hexane), the desired cyclopropyl vinyl ketone **2-97** (356 mg, 39% yield) was given as a colorless oil. *E/Z ratio = 3.57:1*. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.23 - 7.19 (m, 1.34 H), 7.17 - 7.11 (m, 2.46 H), 6.82 - 6.77 (m, 3.36 H), 6.77 - 6.71 (m, 3.00 H), 6.65 - 6.62 (m, 1.00 H), 5.60 - 5.55 (m, 0.28 H), 3.81 - 3.80 (m, 1.10 H), 3.80 (s, 2.69 H), 3.78 (s, 3.38 H), 3.41 (t, *J* = 8.7 Hz, 0.30 H), 3.35 (s, 0.78 H), 3.33 - 3.27 (m, 3.81 H), 2.74 - 2.69 (m, 1.99 H), 2.67 - 2.64 (m, 0.57 H), 2.61 - 2.46 (m, 2.61 H), 2.29 - 2.25 (m, 0.39 H), 2.22 (dd, *J* = 4.9, 7.9 Hz, 0.95 H), 1.93 - 1.92 (m, 0.75 H), 1.82 (d, *J* = 1.2 Hz, 2.77 H), 1.70 - 1.65 (m, 0.29 H), 1.44 (dd, *J* = 4.9, 9.2 Hz, 0.96 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 196.0, 169.2, 159.7, 158.6, 142.5, 141.2, 137.2, 129.9, 129.4, 127.0, 120.7, 114.1, 113.4, 111.4, 55.1, 52.0, 41.4, 34.6, 30.5, 29.7, 19.8, 12.1. **IR:** 2949 (w), 1732 (m), 1664 (m), 1610 (m), 1516 (s), 1246 (s) cm^{-1}. **HRMS (EI)** m/z: $[M]^+$ Calcd. for $C_{25}H_{28}O_5$ 408.1937; Found 408.1934.



2-106

Methyl (1*R*,4a*S*,10a*R*)-7-methoxy-1-(4-methoxyphenyl)-4a-methyl-4-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-3-carboxylate: Cyclopropane **2-97** (100 mg, 0.245 mmol) was dissolved in DCM (4.9 mL) with 4Å molecular sieves and $SnCl_4$ (6 µL, 0.049 mmol) was added. The reaction was stirred for 3 hours and quenched with water. The mixture was extracted three times with DCM, washed with brine, dried over

Na_2SO_4, filtered through celite, and concentrated. The crude residue was purified by flash chromatography (R_f = 0.33, 20% EtOAc/Hexane) to give **2-106** (25 mg, 25% yield) as a colorless oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.17 - 7.12 (m, 2 H), 6.89 - 6.85 (m, 2 H), 6.78 - 6.75 (m, 2 H), 6.73 - 6.71 (m, 1 H), 3.82 - 3.79 (m, 6 H), 3.76 - 3.74 (m, 3 H), 3.68 (dd, *J* = 5.2, 13.4 Hz, 1 H), 3.00 - 2.88 (m, 2 H), 2.68 (dd, *J* = 6.7, 18.0 Hz, 1 H), 2.31 - 2.12 (m, 3 H), 1.91 - 1.82 (m, 1 H), 1.47 - 1.40 (m, 4 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 208.7, 170.5, 158.4, 158.3, 135.8, 135.2, 129.9, 128.2, 114.7, 114.1, 113.2, 55.2, 55.2, 54.2, 53.5, 52.0, 48.3, 40.6, 37.7, 27.0, 24.2, 20.4. **IR:** 2949 (w), 2837 (w), 1742 (m), 1705 (m), 1609 (m), 1512 (m), 1242 (s) cm^{-1}. **HRMS (EI)** m/z: $[M]^+$ Calcd. for $C_{25}H_{28}O_5$ 408.1937; Found 408.1945.

2.11.4 NMR Spectra

Acquisition Time (sec)	3.2768	***Comment***	5 mm PABBO BB/19F-1H/D Z-GRD Z113652/0157			***Date***	24 Mar 2016 12:55:28
Date Stamp	24 Mar 2016 12:55:28			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-11A-T2\3\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	105.59	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.3035	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	22.799

CWW-III-11A-T2-1H.esp

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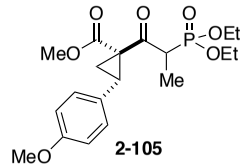

2-105

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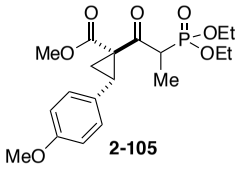

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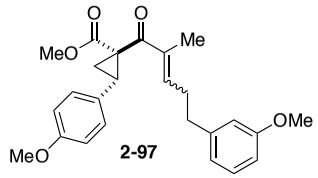

2-97

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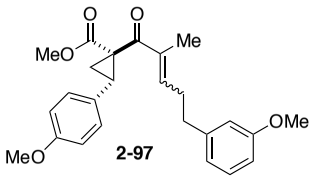

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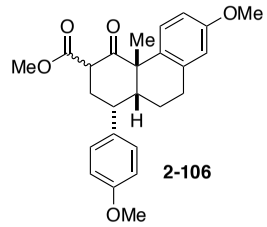

2-106

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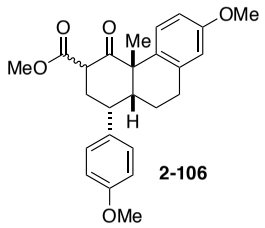

2-106

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CHAPTER 3. PROGRESS TOWARD THE SYNTHESIS OF PROPOLISBENZOFURAN B

3.1 Propolis: From Alternative Medicine to Attractive Natural Product Source

Not to be confused with beeswax, propolis is a strongly adhesive resin collected by bees from a number of botanical sources. It is collected by bees and mixed with various salivary enzymes, beeswax, and other digested material, and is used for the strengthening of the honeycomb and preventing the entrance of intruders into the hive (hence its alternative name, bee glue). Because propolis is formed from various botanical sources, the composition of propolis used in hives differs greatly depending on the plants from which it is sourced. For example, propolis obtained from temperate zones, such as Europe, contain mostly phenolic compounds and flavonoids (Figure 3.1A);[1] however, propolis obtained from tropical zones contain vastly different molecular architectures, such as labdane diterpenoids (Figure 3.1B).[2] Dating back as far as 300 B.C.,[3] propolis has been reputed to have a number of potent biological properties, including antiseptic, antifungal, anti-inflammatory, antioxidant, and anesthetic properties.[4] Propolis and its extracts are currently in use across the globe in many alternative medicine products, mostly for dermatological applications. Because of propolis's reputation for biological activity, the natural products within propolis extracts have become an attractive target as new therapeutic compounds.

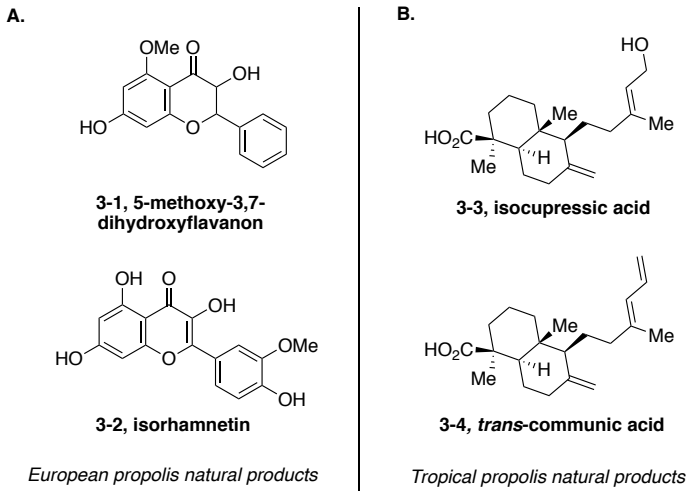
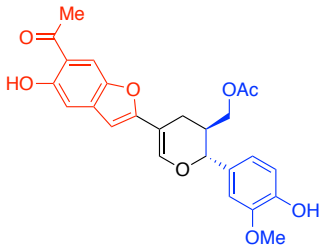
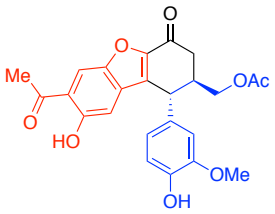


Figure 3.1 Different Molecular Architectures within Propolis from Different Areas

Brazilian propolis in particular has become a plentiful source of bioactive molecules, with its phytochemical diversity most attributed to the number of types of propolis found within the country. Many different compounds have been isolated from Brazilian propolis, including the anti-inflammatory agents apigenin, artepillin C, and many others.[5] In 2000, two novel benzofuran natural products, propolisbenzofurans A and B (Figure 3.2), were isolated from Brazilian propolis and were found to have modest cytotoxic effects toward liver-metastatic murine colon 26-L5 carcinoma (12.4 and 13.7 μg/mL, respectively) and human HT-1080 fibrosarcoma (13.9 and 43.2 μg/mL, respectively).[6] However, like many other natural products, propolisbenzofurans A and B do not exist in great abundance from the crude material from which they were extracted. From 1.8 kilograms of raw Brazilian propolis, only 7 milligrams of Propolisbenzofuran A and 18.2 milligrams of propolisbenzofuran B were obtained. As such, more extensive investigation into the bioactive properties of these two molecules is not feasible if only obtained by mere extraction methods.



3-5, Propolisbenzofuran A
Colon Carcinoma ED_{50} = 12.4 μg/mL
Fibrosarcoma ED_{50} = 13.9 μg/mL



3-6, Propolisbenzofuran B
Colon Carcinoma ED_{50} = 13.7 μg/mL
Fibrosarcoma ED_{50} = 43.2 μg/mL

Figure 3.2 Propolisbenzofurans A and B

Propolisbenzofuran A possesses a central 3,4-dihydro-2*H*-pyran core scaffold, with one of the major substituents consisting of a 5-hydroxy-6-acetylbenzofuran (shown in red, Figure 3.2) attached at its 2-position, and the other two substituents appearing to derive from an acetylated ferulic alcohol in a *trans* configuration across the pyran ring (shown in blue, Figure 3.2). Propolisbenzofuran B, on the other hand, possesses a rather unique 5-hydroxy-6-acetylbenzofuran-fused cyclohexanone (shown in red) core scaffold, with the other two substituents again being derived from an acetylated ferulic alcohol in a *trans* configuration across the cyclohexanone ring (shown in blue). Because of its unique heteroaryl-fused cyclohexanone core, modest anticancer potency, and the need for further biological investigations, propolisbenzofuran B remains an attractive target to synthetic chemists.

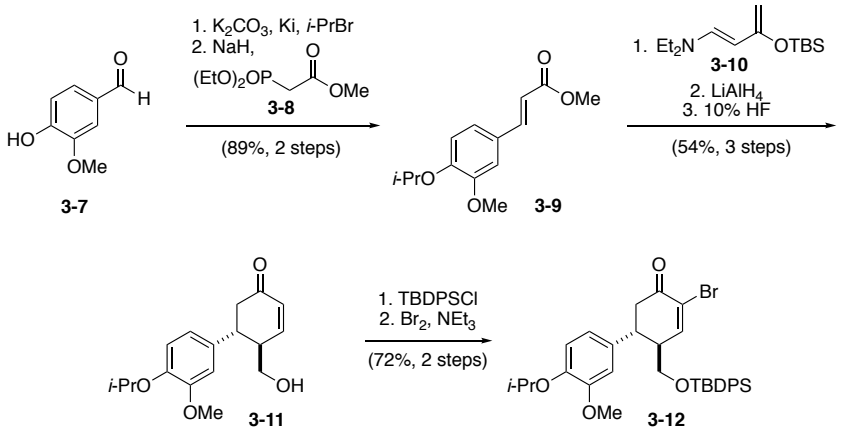
3.2 Previous Synthetic Efforts Toward Propolisbenzofuran B

As an attractive target to synthetic chemists, two groups thus far have synthesized propolisbenzofuran B, each within the last five years. The first synthesis was published in 2014 by Thomson and co-workers;[7] this synthesis featured a CAN-mediated oxidative coupling between two silyl tethered enolates as a key step. The majority of the synthesis will be discussed in detail in Chapter 3.2.1. The second synthesis of propolisbenzofuran

B was published in 2017 by Ramana and co-workers;[8] this synthesis featured a rhodium-catalyzed intramolecular hydroacylation as the key step to form the benzofuran fused cyclohexanone core. The majority of this synthesis will also be discussed in detail in Chapter 3.2.2.

3.2.1 Thomson's Synthesis of Propolisbenzofuran B[7]

Although Thomson and co-workers were forced to retool their original synthesis to accompany a failed late-stage Fries acylation, a great majority of their synthetic sequence remained the same. To begin the synthesis (Scheme 3.1), Thomson and co-workers began by first alkylating vanillin with isopropyl bromide, followed by a Horner-Wadsworth-Emmons reaction with methyl diethylphosphonoacetate to form the methyl ferulic ester derivative **3-9**. This ferulic ester was then heated with the Rawal-Kozmin diene **3-10** to undergo a Diels-Alder cycloaddition to form a cyclic enol ether, followed by reduction of the ester with $LiAlH_4$ and removal of the TBS protecting group/elimination of diethylamine to form cyclohexenone **3-11**. Protection of the primary alcohol followed by bromination formed the vinyl bromide **3-12** in 72% yield over 2 steps. This vinyl bromide would serve as a major fragment of the molecule as part of a convergent synthetic sequence.

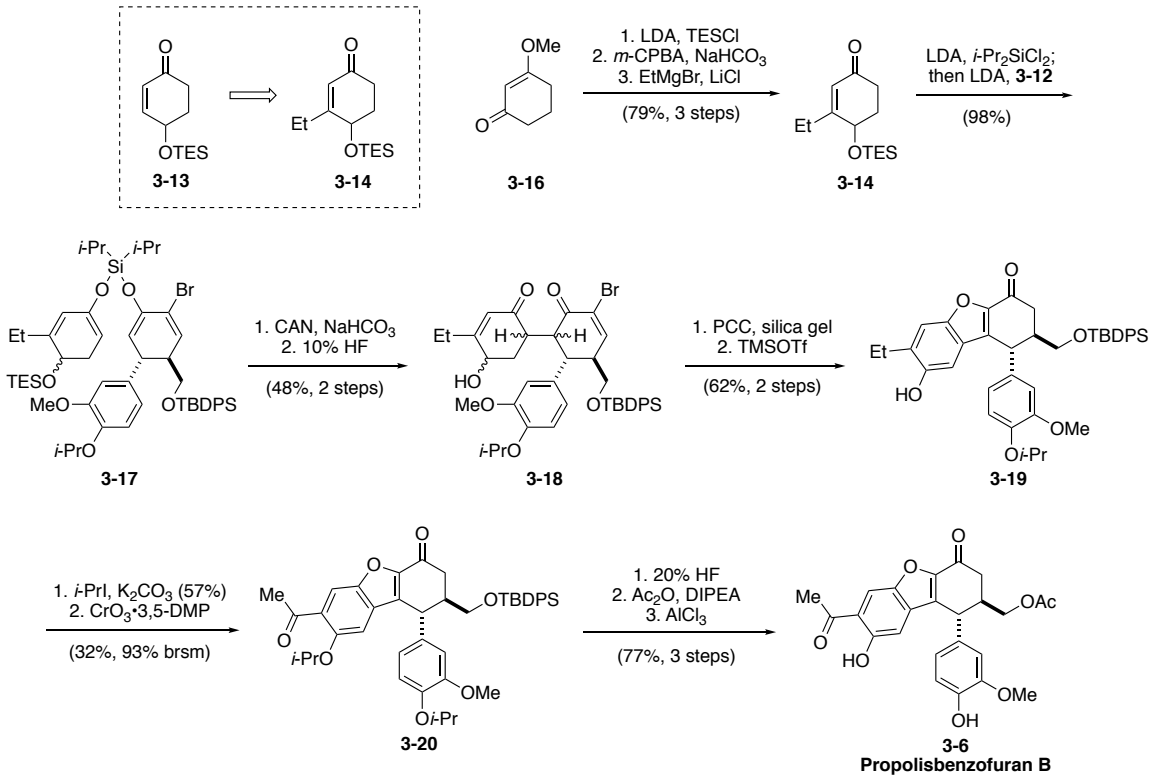


Scheme 3.1 Thomson's Vinyl Bromide Fragment

Thomson's retooling came from the failure of a late stage Fries acylation of the benzofuran, originating from cyclohexenone **3-13**. However, from simply adding an ethyl group to form **3-14**, oxidation of the benzylic methylene unit to a ketone would later provide the desired natural product. Compound **3-14** is readily accessible from a three-step sequence from the commercially available cyclic vinyligous ester **3-16**, giving 79% yield over three steps. From **3-14**, formation of the silyl enol ether, followed by reaction of the enolate of **3-12** gives the asymmetric silyloxy compound **3-17** in 98% yield. In the next step, Thomson demonstrated an oxidative coupling using ceric ammonium nitrate (CAN) between two enolates tethered by a silyl group to form the stereoisomeric mixture of 1,4-diketone **3-18**. This isomeric mixture, however, was no unpleasant consequence, as the only important stereocenters were previously set in the Diels-Alder step. Gratifyingly for Thomson's group, this oxidative coupling step represented a key methodological showcase for some of their previous work.[9-11]

After removal of the TES protecting group, oxidation with PCC on silica gel formed a dihydroquinone which, when exposed to TMSOTf, undergoes a benzannulation to form the desire benzofuran-fused cyclohexanone **3-19** after acid workup. Following

this second key step, masking of the benzofuran alcohol with an isopropyl group allowed for a clean chromium-mediated oxidation of the benzylic methylene to the desired ketone, **3-20**, in 32% isolated yield. Despite all attempts to increase yield, including higher oxidant loading, increasing temperature, and prolonging reaction times, no increase in yield was observed. However, the benzylic oxidation was a clean reaction that gave a 93% yield based on recovered starting material. The final three steps involved simply removing protecting groups and adding other simple functionality. The TBDPS ether was removed using 20% hydrofluoric acid, and addition of an acetyl group to the corresponding alcohol with acetic anhydride followed. Finally, removal of the aryl isopropyl ethers with $AlCl_3$ provided the desired natural product **3-6** in 77% yield over the final three steps. This represented the first documented synthesis of propolisbenzofuran B, occurring over 17 steps in the longest linear sequence at 2.2% overall yield (Scheme 3.2).



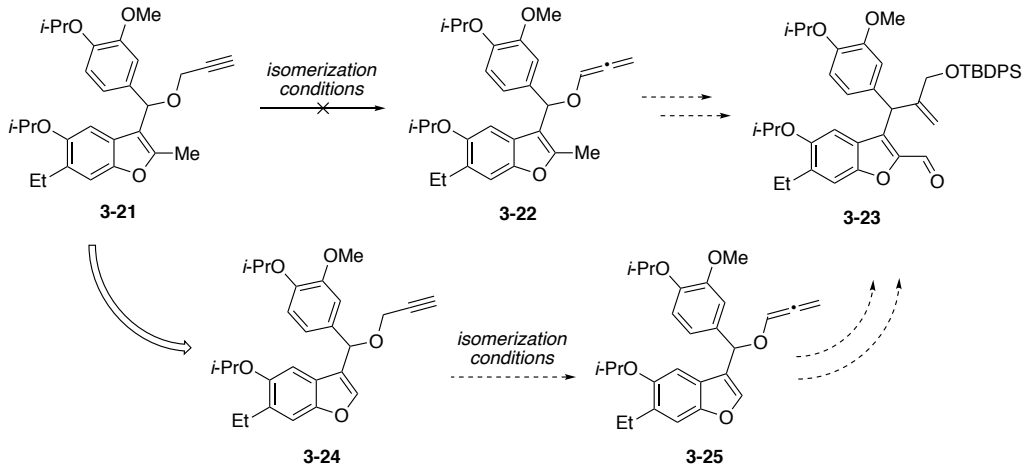
Scheme 3.2 Thomson's Final Synthetic Sequence Toward Propolisbenzofuran B

While Thomson's synthesis was the first reported in the literature for propolisbenzofuran B, several disadvantages were evident. Despite being a rather simplistic structure (only two stereocenters), this synthesis suffered from a rather long synthetic sequence plagued by the necessity of a number of protection/deprotection sequences, and two low-yielding steps were observed in the latter stages of the synthesis (steps 9 and 14). With these things in mind a shorter, higher yielding, and more modular synthetic route would be a great step forward for the synthesis of this natural product.

3.2.2 Ramana's Synthesis of Propolisbenzofuran B[8]

Much like Thomson's pioneering synthesis of propolisbenzofuran B, the second synthesis of the natural product by Ramana and co-workers required much revision within the synthetic route (Scheme 3.3). In this work, it was originally envisioned that

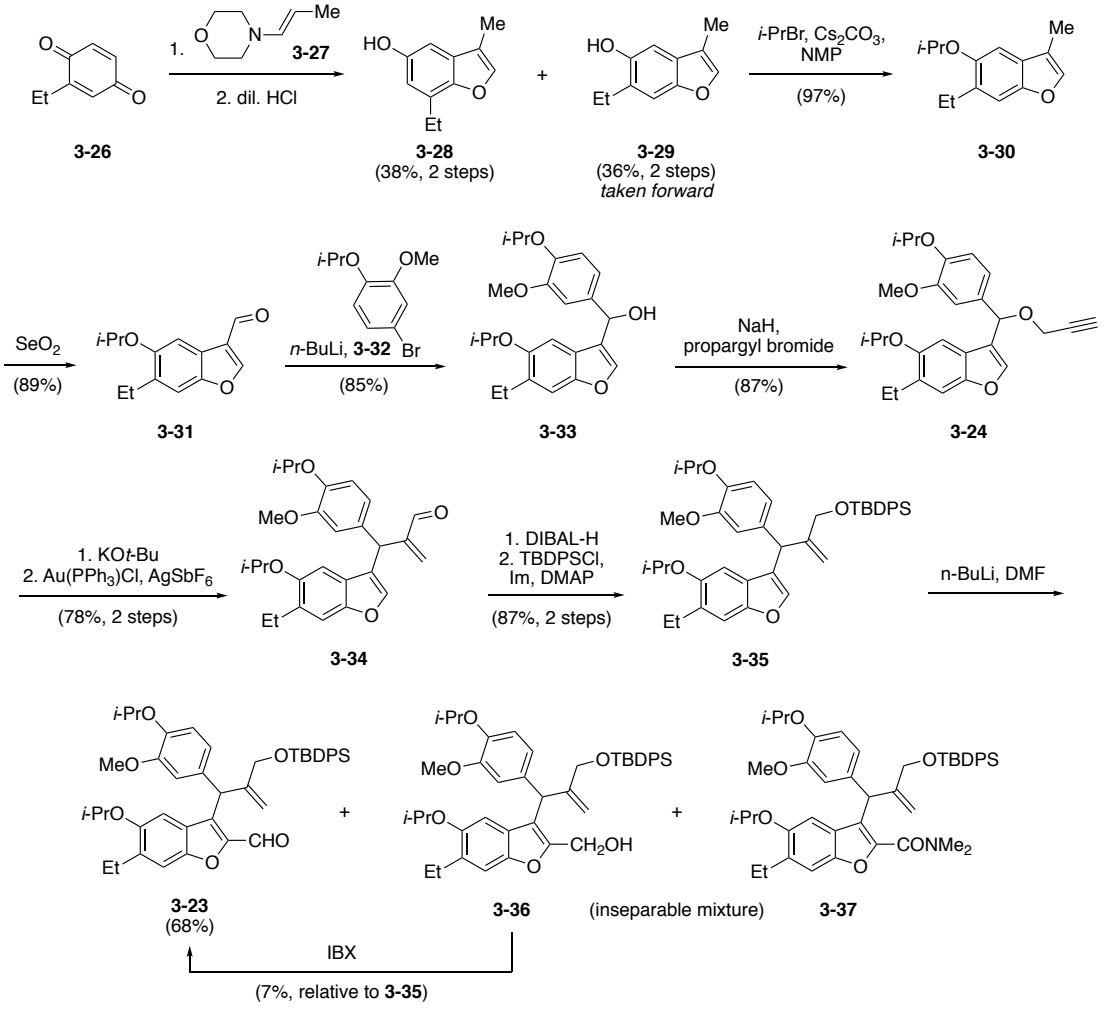
propargyl alcohol **3-21** would undergo a base-mediated allene ether formation to **3-22**, which would be taken forward for a [1,3]-O→C rearrangement and subsequent steps to form **3-23**. However, with methyl substitution at the 2-position of the benzofuran, the propargyl ether isomerization failed under all condition examined. As such, the subsequent desired carbonyl would have to be installed at a later stage. Conditions to promote the desired isomerization would be examined on benzofuran **3-24**, with a hydrogen atom at the 2-position.



Scheme 3.3 Ramana's Required Synthetic Revisions Toward Propolisbenzofuran B

Ramana's synthesis begins (Scheme 3.4) with the condensation of ethyl benzoquinone **3-25** with the trans-morpholine enamine of propionaldehyde, **3-27**, to form the hydroxybenzofurans **3-28** and **3-29** in 38% and 36% yields respectively over two steps. However, the only relevant isomer to the synthesis was **3-29**, which was taken forward for hydroxyl protection by isopropyl bromide to form **3-30**. After a SeO_2-mediated oxidation to aldehyde **3-31**, attack by the lithiated arene **3-32** provided the desired alcohol in relatively high yield over two steps. Alcohol **3-33** was then subjected to propargylation to **3-24** in 87% yield, followed by an allene isomerization and a key [1,3]-O→C rearrangement sequence to form the enal **3-34** in 78% yield over two steps.

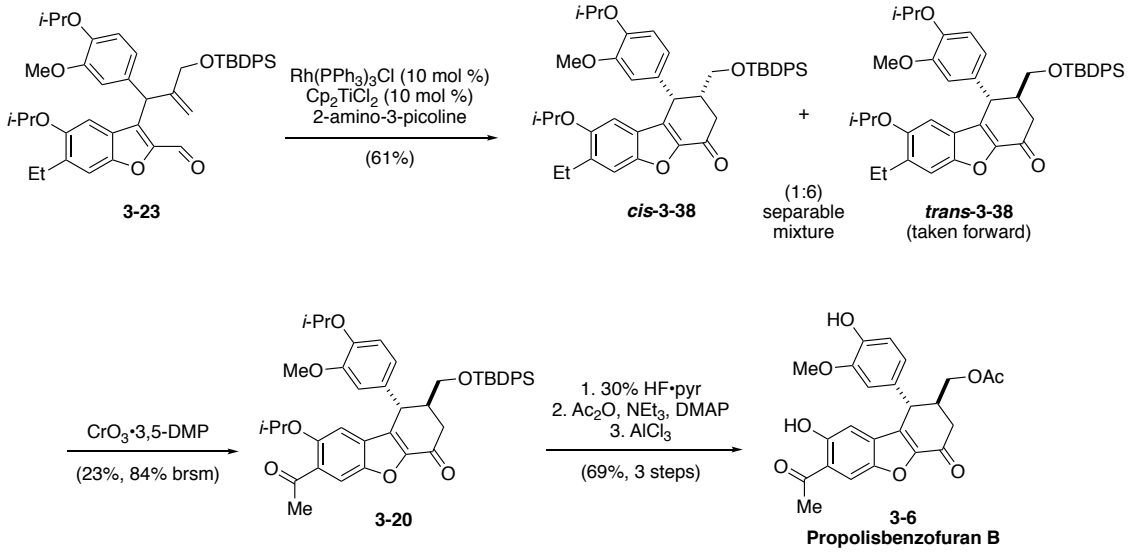
The enal was then reduced with DIBAL-H and protected with TBDPSCl to form **3-35** in 87% yield over two steps. Deprotonation of the benzofuran with n-BuLi and attack on DMF proceeded relatively smoothly, giving key intermediate **3-23** in 68% yield. However, alcohol **3-36** was obtained as an inseparable mixture with amide **3-37**. This was of little consequence because after subjection to IBX, the desired aldehyde **3-23** was separately recovered.



Scheme 3.4 Generation of Key Annulation Intermediate **3-23**

Following the formation of intermediate **3-23**, it was subjected to the next key step, an intramolecular, rhodium-catalyzed olefin hydroacylation with Wilkinson's catalyst in the presence of Cp_2TiCl_2 and 2-amino-3-picoline. This reaction afforded the

benzofuran-fused cyclohexanone **3-38** in a moderate 61% yield a 6:1 *trans*:*cis* diastereomeric mixture. After separation by preparative HPLC, the *trans* isomer was then subjected to essentially the same 4-step reaction sequence as in Thomson's report to complete the synthesis (Scheme 3.5). This represented only the second and most recent synthesis of propolisbenzofuran B, with Ramana and co-workers completing the molecule in 16 steps in the longest linear sequence and 1.0% overall yield (based on isolated yields).



Scheme 3.5 Ramana's Final Steps to Propolisbenzofuran B

Ramana's synthesis demonstrated the first example of the construction of a 4,5-disubstituted cyclohexanone scaffold using a rhodium-catalyzed intramolecular olefin hydroacylation. This method provided a unique and complementary approach to Thomson's oxidative coupling/benzannulation sequence. However, Ramana's synthesis suffered from many of the same disadvantages as Thomson's synthesis, such as low-yielding steps (especially late in the sequence) and a series of protection/deprotection steps. It also suffered from low diastereoselectivity and a number of difficult separations, with the key benzannulation requiring preparative HPLC to attain ***trans*-3-38**. With these

drawbacks in mind, a more diastereoselective, functionality-tolerant, and higher yielding route could be designed to alleviate such issues.

3.3 Homo-Nazarov Cyclizations: Access to Heteroaryl-Fused Cyclohexanones

As mentioned previously in Chapter 1.6, homo-Nazarov reactions have been used previously as a method to access (hetero)aryl-fused cyclohexanones by several groups.[12-15] In Yadav's original 2008 report with substrates of this kind,[12] approximately 10 substrates are shown with high yield and broad substrate scope; unfortunately, four equivalents of the toxic Lewis acid $SnCl_4$ are required, even at high temperatures. In Waser's methodological report,[13] 20 mol % tosic acid is used to activate DACPs toward homo-Nazarov cyclization reactions. However, of the only two examples utilizing heteroaryl cyclopropyl ketones, only N-methylindoles are efficacious. In France's report,[15] 15 examples of heteroaryl cyclopropyl ketones are effective, with (benzo)thiophenes, (benzo)furans, and *N*-methylindoles shown as competent substrates. With these publications in mind, we believed that a homo-Nazarov cyclization approach would represent a faster and more modular route to propolisbenzofuran B that would alleviate many of the issues found in the previous two syntheses.

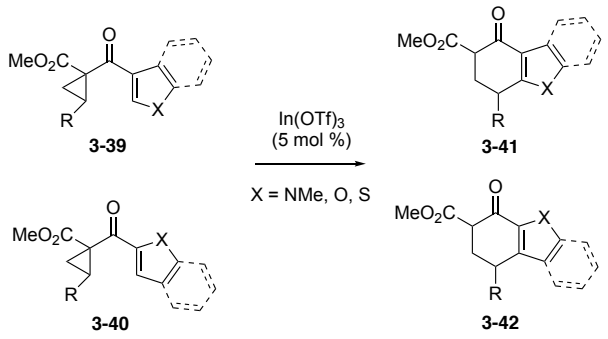
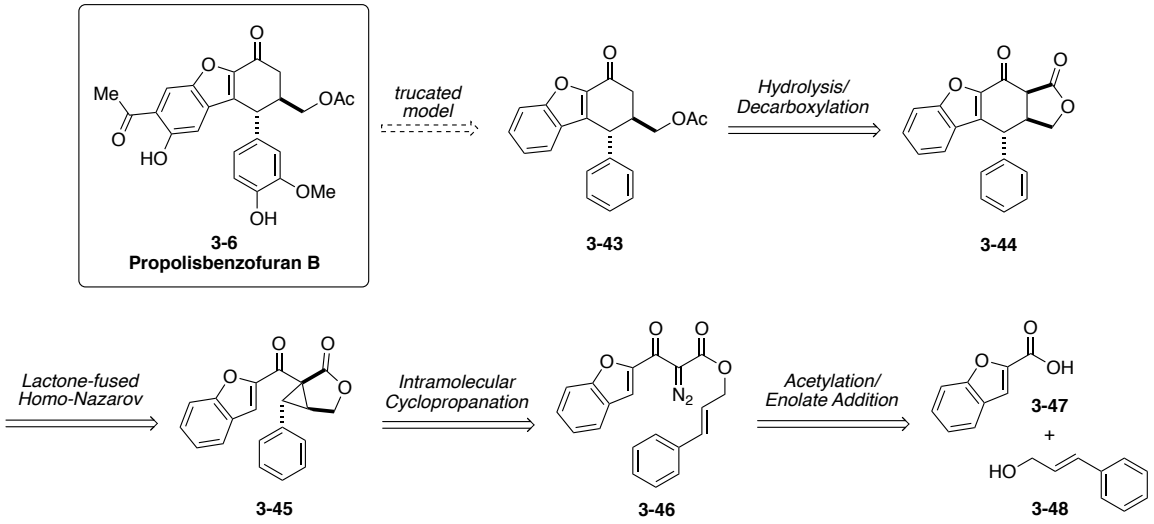


Figure 3.3 France's Previous Homo-Nazarov Cyclization with Heteroaryl Cyclopropyl Ketones

3.4 A Homo-Nazarov Approach Toward Propolisbenzofuran B

3.4.1 Raynold Shenje's Previous Undertaking of a Homo-Nazarov Route

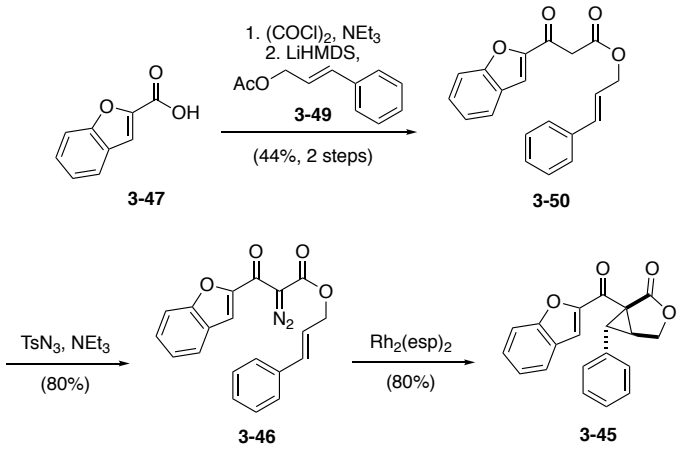
In the France group's first attempt at synthesizing propolisbenzofuran B, Raynold Shenje devised a retrosynthetic analysis that utilized the donor-acceptor-acceptor cyclopropanes that are a hallmark of France's homo-Nazarov chemistry (Scheme 3.6). In this synthetic route, Shenje envisioned gaining proof-of-concept through the truncated model **3-43**. The heteroaromatic-fused cyclohexanone would be assembled via a hydrolysis/ decarboxylation sequence from the tetracyclic lactone **3-44**. Tetracyclic lactone would be assembled via the key step of the synthesis, a homo-Nazarov cyclization of lactone-fused cyclopropane **3-45**. Compound **3-45** is synthesized from an intramolecular cyclopropanation of diazo **3-46**, which is quite readily accessed from commercially available 2-benzofuran carboxylic acid and *trans*-cinnamyl alcohol.



Scheme 3.6 Shenje's Retrosynthetic Analysis of Propolisbenzofuran B

Armed with a logical synthetic route, Shenje set out first to synthesize cyclopropane **3-45** (Scheme 3.7). Firstly, **3-47** was converted to an acid chloride with

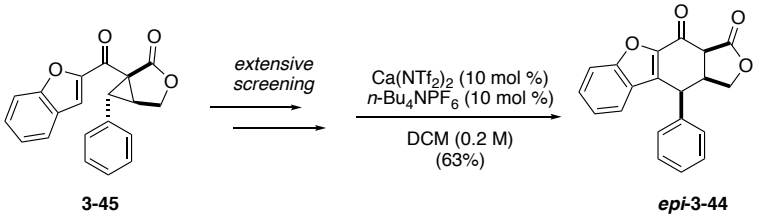
oxalyl chloride and triethylamine. Acetylated cinnamyl alcohol was deprotonated with LiHMDS, and then reacted with the acid chloride of **3-47** to form β-ketoester **3-50** in 44% yield over two steps. This β-ketoester was then subjected to diazo transfer condition with tosyl azide and triethylamine to give the α-diazo-β-ketoester **3-46** in 80% yield, which was taken forward for a rhodium-catalyzed intramolecular cyclopropanation with $Rh_2(esp)_2$ to obtain the desired lactone-fused cyclopropane **3-45** in 80% yield.



Scheme 3.7 Shenje's Synthesis of Lactone-Fused Cyclopropane **3-45**

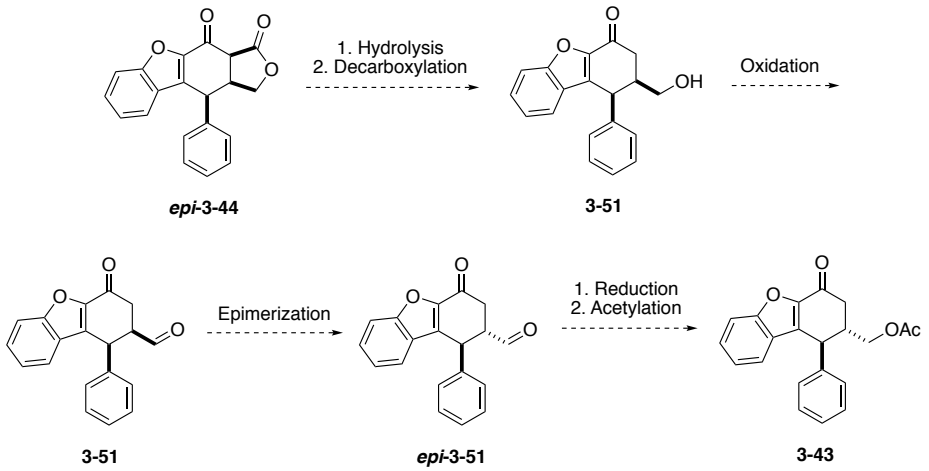
Next, Shenje set out to evaluate the feasibility of the key-step of his synthetic sequence, the homo-Nazarov reaction to generate the benzofuran-fused cyclohexanone **3-44**. After an extensive Lewis acid, concentration, and concentration screen, Shenje discovered the optimized conditions for reactivity were 10 mol % $Ca(NTf_2)_2$, 10 mol % *n*-Bu_4NPF_6 in DCM at 0.2 M producing the desired cyclohexanone in 63% yield.[16] However, a rather unexpected result was also obtained – inversion of stereochemistry at the benzylic position to give cyclohexanone ***epi*-3-44** (Scheme 3.8). This stereochemical outcome can be attributed to the polar mechanism of the ring-opening/ring-closing cyclization process. Upon ring opening, a carbocation is formed at the benzylic carbon.

This planar carbocationic species can be attacked from either face, resulting in loss of the desired stereochemical outcome.



Scheme 3.8 Shenje's Homo-Nazarov Cyclization Outcome

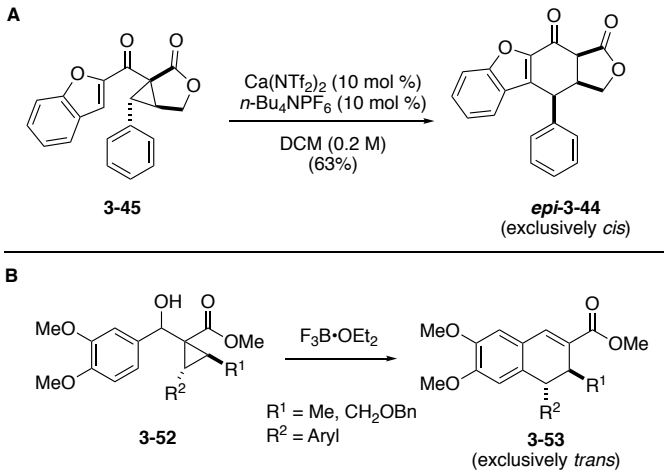
While this result was not ideal, it did not deter Shenje from designing a new strategy toward propolisbenzofuran B in subsequent steps. The synthesis of *epi*-propolisbenzofuran B could be achieved through this route, and upon synthesis of the benzofuran-fused cyclohexanone ***epi*-3-44**, a sequence of steps could be employed to afford the desired stereochemical outcome (Scheme 3.9): (1) a hydrolysis/decarboxylation sequence to afford the alcohol **3-51**, (2) compound **3-51** would be oxidized to an aldehyde, (3) a base-mediated epimerization would afford the trans diastereomer ***epi*-3-51**, and finally (4) a reduction/acetylation sequence would then give compound **3-43**. All steps would be expected to translate to the non-truncated substrate, as no steps in the epimerization sequence would interfere with the added functionality. While this sequence would alleviate the stereochemical issue at hand, it adds three extra linear steps to the route, which would negatively affect overall yield. As such, a major revision to the retrosynthetic analysis of the natural product to avoid stereochemical issues altogether would be greatly beneficial.



Scheme 3.9 Revisions Toward the Desired Stereochemical Outcome

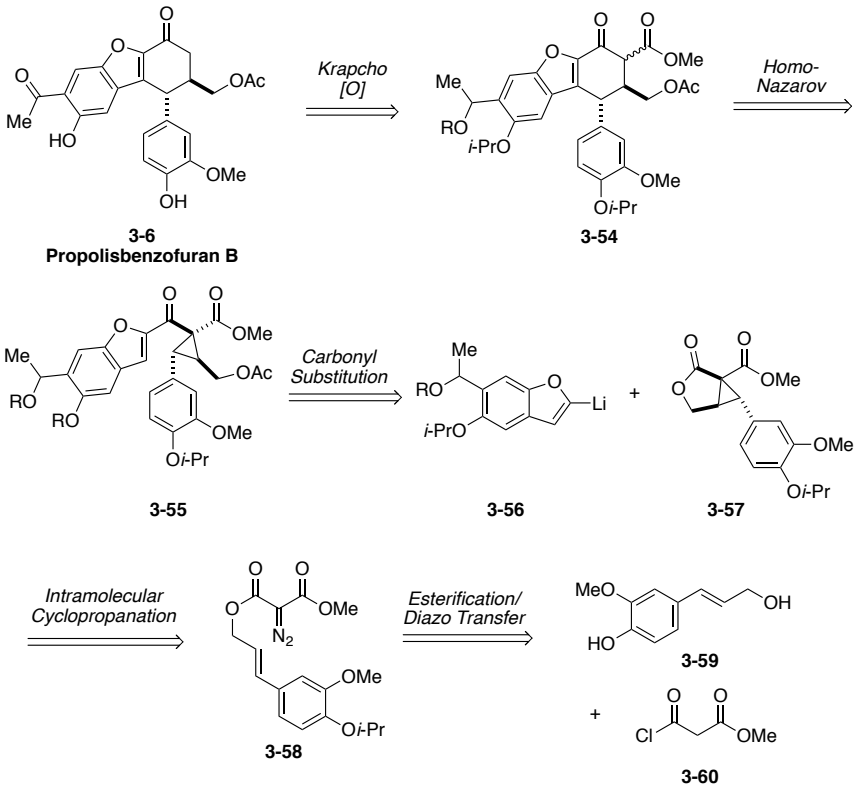
3.4.2 Revising the Route to Propolisbenzofuran B: A Trans-Selective Outcome

As Shenje's route gave the undesired stereochemical outcome of the homo-Nazarov reaction and steps began to add up, we began to revise our synthetic route toward propolisbenzofuran B. One hypothesis was that fused lactone greatly influenced the stereochemical outcome of the key homo-Nazarov cyclization step. As such, we first revised our synthesis to exclude the use of a lactone-fused cyclopropane in the homo-Nazarov step (Scheme 3.10A) and include a vicinally disubstituted cyclopropane. We envisioned that this would remove any torsional influence forcing attack from a single face to afford undesired *cis* diastereomers, as precedented in Nishii's dehydrative homo-Nazarov work (Scheme 3.10B).[17-18]



Scheme 3.10 Shenje's Previous Work vs. Nishii's Stereoselective Cyclization

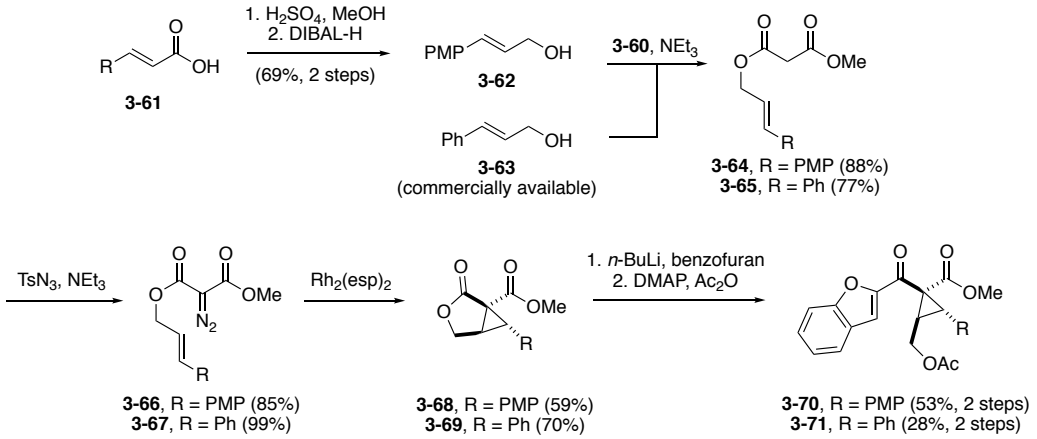
We began designing a synthetic route of propolisbenzofuran via the retrosynthetic analysis shown in Scheme 3.11. The ketone as the 6-position of the benzofuran would be installed by oxidation of a benzyl alcohol, while the ester group would be removed via a Krapcho decarbalkoxylation from **3-54**. Cyclohexanone **3-54** would be obtained from the key step of the synthesis, a homo-Nazarov cyclization of cyclopropane **3-55**. The key cyclopropane intermediate is accessed from lithiated benzofuran **3-56** and the lactone-fused cyclopropane **3-57**. The lactone-fused cyclopropane would be synthesized from a rhodium-catalyzed intramolecular cyclopropanation from diazo **3-58**, much like that in Shenje's previous route. The diazo would be prepared from a diazo transfer of the diester formed from ferulic alcohol **3-59** and methyl malonyl chloride. This route, we believed, would alleviate many of the issues in Shenje's previous undertaking, avoiding the oxidation/epimerization/reduction/ acetylation sequence altogether. This revised route also would provide a more convergent strategy, dividing the molecule into two major fragments: the cyclopropane and benzofuran fragments. This convergent strategy would provide potential for the rapid synthesis of unnatural analogs as well. Armed with this revised synthetic route, we began our synthetic journey toward propolisbenzofuran B.



Scheme 3.11 Revised Synthetic Route Toward Propolisbenzofuran B

In order to gain insight into the diastereoselectivity of our key homo-Nazarov step, we began preparing two truncated model systems using phenyl and PMP as cyclopropyl donors, although PMP would better represent the electronics of the actual system (Scheme 3.12). 4-Methoxy cinnamyl alcohol was prepared from 4-methoxy cinnamic acid **3-61** through an esterification with methanol/reduction with DIBAL-H sequence in 69% yield over 2 steps. The two methyl cinnamyl malonate esters **3-64** and **3-65** were prepared from methyl malonyl chloride in the presence of triethylamine. From this point, the appropriate diazo compounds were prepared using tosyl azide, and subsequent cyclopropanations occurred in 59% and 70% yield for the PMP (**3-68**) and Ph (**3-69**) substrates, respectively. From Nishii's previous work, it had been shown that lithiated arenes attack the lactone portion of similar cyclopropanes, so we proceeded with a similar reaction of benzofuran on our lactone-fused cyclopropanes.[18] Succeeding

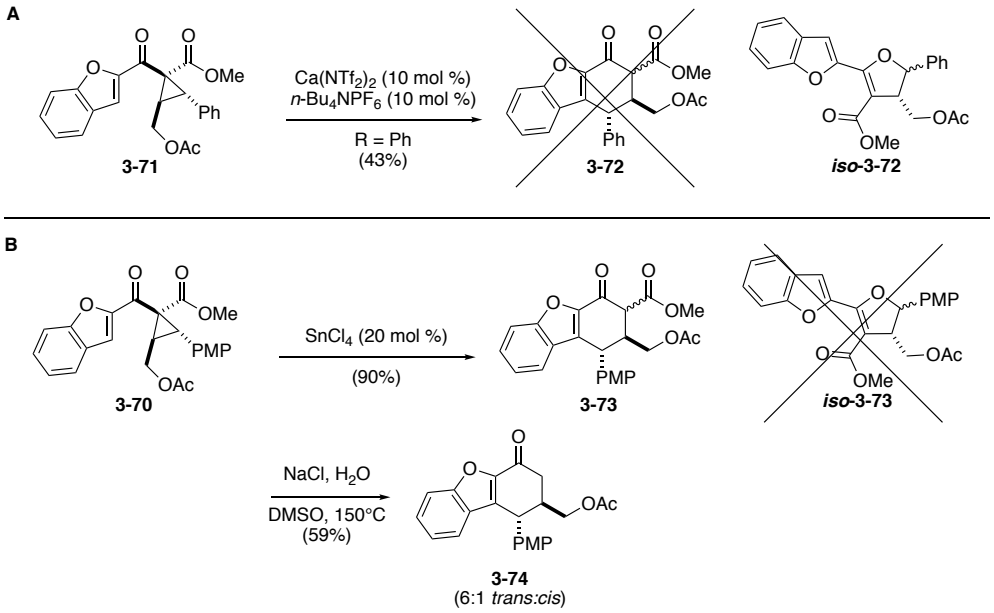
acetylations were then performed on the resulting alcohols to give the desired cyclopropanes **3-70** and **3-71**.



Scheme 3.12 Preparation of Truncated Cyclopropyl Substrates

Following this, we proceeded to test the viability of these cyclopropyl substrates toward the desired homo-Nazarov reactivity. Upon exposing the phenyl cyclopropane **3-71** to Shenje's optimized conditions, an undesired dihydrofuran (DHF) isomer was isolated with no desired benzofuran-fused cyclohexanone detected (Scheme 3.13A). At this point, we believed that this result was a function of the calcium catalyst system rather than the substrate. However, all studies from this point forward were conducted on the PMP-substituted cyclopropane substrate, as it should provide a better representation of the electronics on the elaborated substrate. From our previous studies in Chapter 2, and previous literature precedence that $SnCl_4$ could transform DHF substrates into the desired cyclohexanones,[19] we believed that $SnCl_4$ would provide a better environment for the desired reactivity. Gratifyingly, upon subjecting cyclopropane **3-70** to 30 mol % $SnCl_4$, the desired benzofuran-fused cyclohexanone **3-73** was obtained in 90% yield, with no DHF isomer detected. Following this, a Krapcho decarbalkoxylation was performed to determine diastereoselectivity, and the *trans*-isomer of **3-74** was found to be the major

diastereomer at a ratio of ~6:1 (Scheme 3.13B). This provided the proof-of-concept that our revised homo-Nazarov strategy was a viable route to the *trans* substitution observed in propolisbenzofuran B, avoiding the oxidation/epimerization/reduction/acetylation steps required in Shenje's previous strategy altogether.

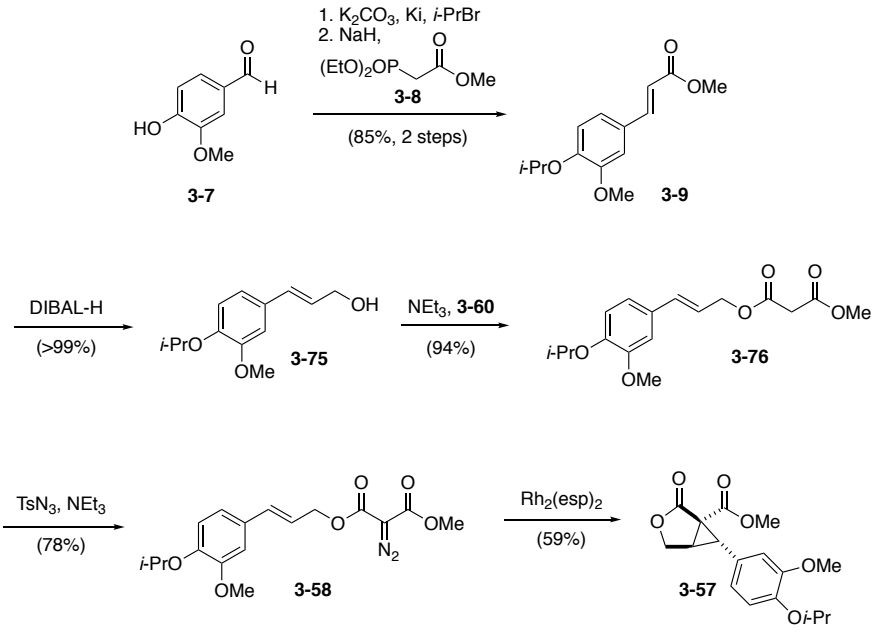


Scheme 3.13 Ring-Opening Cyclizations of Two Catalyst Systems

3.4.3 Progress Toward Propolisbenzofuran B Thus Far

Armed with the knowledge that the revised route gave the desired *trans*-substitution within the natural product, we then set out to synthesize propolisbenzofuran B itself (Scheme 3.14). We began with the synthesis of the cyclopropane fragment **3-57**. We began with vanillin and proceeded with the same alkylation/Horner-Wadsworth-Emmons sequence as Thomson and co-workers to obtain the unsaturated ester **3-9**. Reduction of **3-9** was carried out with DIBAL-H in quantitative yield to give alcohol **3-75**, which was then converted to the methyl ferulic malonyl ester **3-76** with methyl malonyl chloride (**3-60**) in 94% yield. The malonate diester was then subjected to diazo

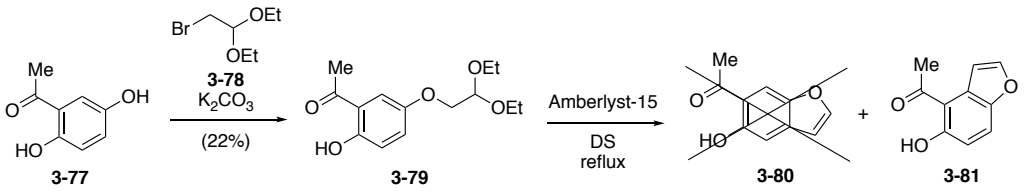
transfer conditions to afford the α-diazo-methyl ferulic malonyl ester **3-58** in 78% yield. Intramolecular cyclopropanation with $Rh_2(esp)_2$ then gave the cyclopropane fragment **3-57** in 59% yield. While many of the steps remain unoptimized, the cyclopropane fragment was obtained in only 6 steps with an overall yield of 36%.



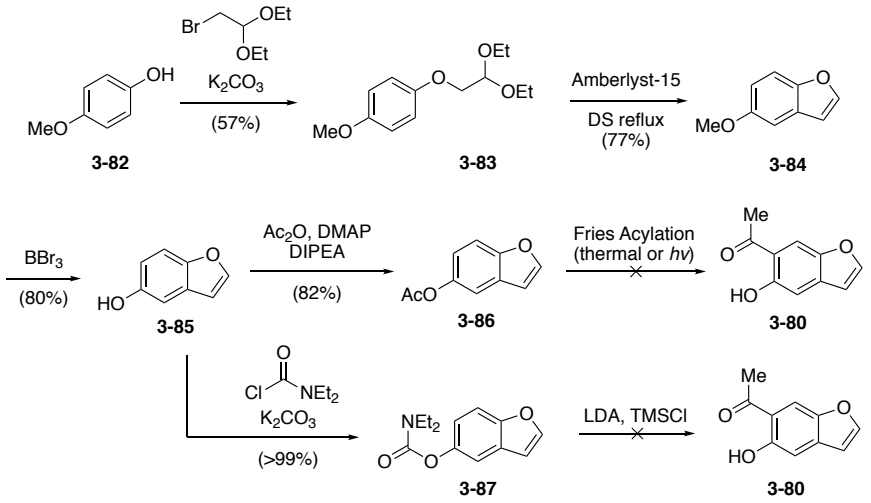
Scheme 3.14 Synthesis of the Cyclopropane Fragment **3-57**

With the cyclopropane fragment in hand, we then proceeded with the synthesis of the benzofuran fragment. Although the needed benzofuran precursor **3-80** had been synthesized several times previously, we had issue replicating the results to obtain **3-80** from any preparations obtained from past literature; only **3-81** was obtained instead (Scheme 3.15).[20-22] Undeterred by this result, we pressed on to find a new route to **3-80** (Scheme 3.16). We began with the alkylation of 4-methoxyphenol with bromoacetaldehyde diester acetal **3-78** to give **3-83**. Following this, annulation to form 5-methoxybenzofuran proceeded smoothly and subsequent demethylation gave 5-hydroxybenzofuran in 80% yield. Two different routes to synthesize 3-80 then proceeded, with the first involving a Fries acetylation. All attempts to perform this

reaction with $AlCl_3$ under thermal or photochemical conditions were unsuccessful. Another route involving the synthesis of carbamate **3-87** was also attempted,[23] although also unsuccessful. Further work to synthesize **3-80** is currently underway by Doris Chen, another graduate student in the France lab.



Scheme 3.15 Attempts to Replicate the Synthesis of **3-80** from Previous Literature

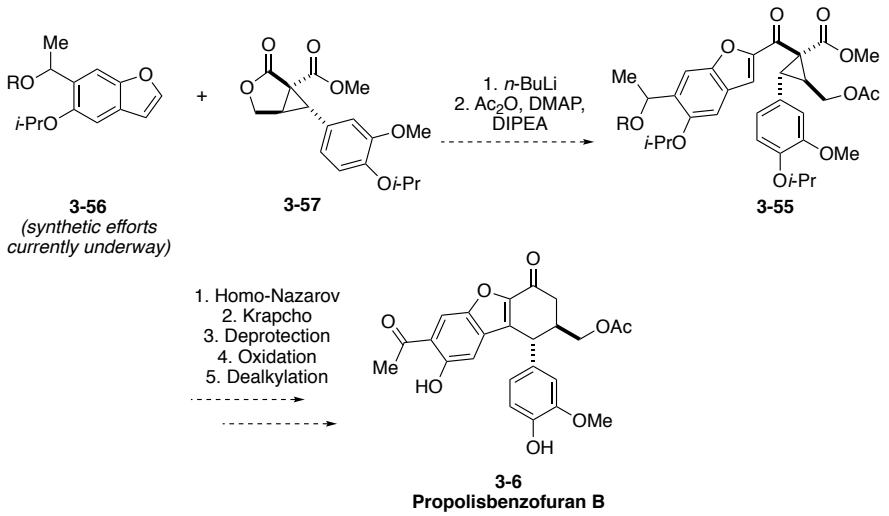


Scheme 3.16 Other Attempts to Synthesize **3-80**

3.5 Summary of Efforts Toward the Synthesis of Propolisbenzofuran B

A novel route utilizing a homo-Nazarov cyclization to access the benzofuran-fused cyclohexanone core of propolisbenzofuran B has been developed. A mildly diastereoselective protocol requiring 30 mol % $SnCl_4$ for the key *trans* stereochemical outcome was investigated, although further optimization in this key step and throughout the synthesis is ongoing. A synthetic sequence to access the key cyclopropane precursor **3-57** has been achieved, although synthesis of the benzofuran fragment **3-56** is also

ongoing. With proof-of-concept of all key steps demonstrated, the total synthesis of the natural product could be envisioned. This convergent approach would allow access to a variety of unnatural analogs of propolisbenzofuran B in the search of key structure-activity relationships. This protocol also demonstrates the potential of homo-Nazarov cyclizations in the total synthesis of natural products containing a cyclohexane core scaffold.



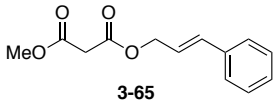
Scheme 3.17 Summary of Efforts Toward Propopolisbenzofuran B Via a Revised Homo-Nazarov Strategy

3.6 Experimental Section

3.6.1 Synthetic Methods

Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-65μm) or preparative thin-layer chromatography (prep-TLC) using Silicycle silica gel F_{254} (1000 μm) plates and solvents indicated as eluent with 1-5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light.

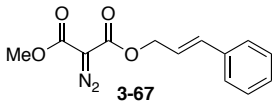
Infrared (IR) spectra were obtained using a Shimadzu IRAffinity-1S FTIR with a Specac Quest ATR attachment. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, or Bruker 400 MHz, 500 MHz, and 800 MHz spectrometers with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer using $PhCF_3$ as an external standard. ^{1}H and ^{19}F NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Mass spectra were obtained MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of 10,000 using PFK (perfluorokerosene) as an internal calibrant. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).



3-65

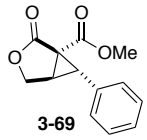
Cinnamyl methyl malonate: Cinnamyl alcohol (0.94 mL, 7.32 mmol) was added to a flask and dissolved in DCM (7.3 mL). Triethylamine (0.61 mL, 4.39 mmol) was added, stirred for 10 minutes, and cooled to 0°C. Methyl malonyl chloride (0.39 mL, 3.66 mmol) was added slowly, and the mixture was warmed to room temperature to stir overnight. The reaction was quenched with sat. aq. $NaHCO_3$, extracted three times with DCM, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.19, 10% EtOAc/Hexane) to give cinnamyl methyl malonate

(652 mg, 77% yield) as a pale yellow oil. Characterization was consistent with that reported.[24]



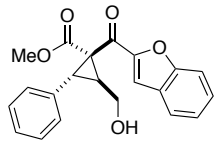
3-67

1-cinnamyl 3-methyl 2-diazomalonate: Cinnamyl methyl malonate (635 mg, 2.71 mmol) was added to a flask and dissolved in MeCN (14 mL). Triethylamine (0.58 mL, 4.15 mmol) was added and the mixture was stirred for 10 minutes. Tosyl azide (0.51 mL, 3.32 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was then concentrated and purified by flash chromatography (R_f = 0.14, 10% EtOAc/Hexane) to give the diazo (703 mg, 99% yield) as a yellow oil. Characterization was consistent with that reported.[25]



3-69

Methyl (1*R*,5*S*,6*R*)-2-oxo-6-phenyl-3-oxabicyclo[3.1.0]hexane-1-carboxylate: $Rh_2(esp)_2$ (9 mg, 0.01 mmol) was added to a flask and dissolved in DCM (100 mL) and cooled to 0°C. 1-cinnamyl 3-methyl 2-diazomalonate (680 mg, 2.61 mmol) was dissolved in DCM (20 mL) and added in one portion at 0°C and warmed to room temperature for 3 hours. The reaction was quenched with sat. aq. thiourea, extracted three times with DCM, washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.16, 20% EtOAc/Hexane) to give the cyclopropyl lactone **3-69** (426 mg, 70% yield) as a waxy white solid. Diastereomeric ratio = >99:1. Characterization was consistent with that reported.[18]

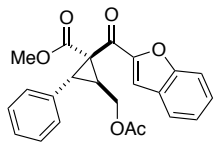


: unknown byproduct

SI-3-1 3.8 : 1

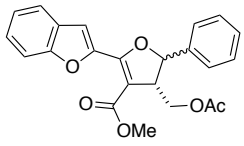
Methyl (1*S*,2*S*,3*R*)-1-(benzofuran-2-carbonyl)-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxylate: Adapted from a previously published procedure.[18] Benzofuran (168 mg, 1.42 mmol) was added to a flask, dissolved in THF (0.37 mL), and cooled to 0°C. n-Butyllithium (0.54 mL, 1.36 mmol) was added dropwise to the solution, stirred for 30 minutes at 0°C, and warmed to room temperature for 1 hour. In a separate flask, cyclopropyl lactone **3-69** (300 mg, 1.29 mmol) was dissolved in THF (4.5 mL) and cooled to 0°C. The benzofuran solution was then cannulated dropwise into the cyclopropyl lactone solution to be stirred at 0°C for 2 hours. An aliquot was removed to be quenched with Ac_2O. The rest of the solution was quenched with sat. aq. NH_4Cl, extracted three times with EtOAc, washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by prep-TLC (R_f = 0.62, 50% EtOAc/Hexane) to give a mixture of compounds **SI-3-1** and an indiscernable byproduct as a 3.8:1 mixture (202 mg, <41% yield) as a colorless oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.73 (td, *J* = 1.1, 7.9 Hz, 1.02 H), 7.65 - 7.61 (m, 1.27 H), 7.60 - 7.57 (m, 1.03 H), 7.55 (dd, *J* = 0.9, 8.2 Hz, 0.29 H), 7.50 (ddd, *J* = 1.2, 7.1, 8.5 Hz, 1.11 H), 7.38 - 7.30 (m, 5.64 H), 7.30 - 7.20 (m, 3.40 H), 7.05 (d, *J* = 0.9 Hz, 0.26 H), 4.47 - 4.43 (m, 0.29 H), 4.20 (d, *J* = 8.5 Hz, 0.28 H), 3.96 (td, *J* = 5.6, 11.9 Hz, 1.08 H), 3.51 (ddd, *J* = 4.6, 8.2, 12.2 Hz, 1.16 H), 3.46 (d, *J* = 7.9 Hz, 1.01 H), 3.38 (s, 3.00 H), 3.35 (s, 0.80 H), 3.14 (dt, *J* = 5.6, 8.3 Hz, 1.32 H), 2.96 - 2.93 (m, 0.27 H), 1.87 (t, *J* = 5.6 Hz, 0.99 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 183.4, 168.2, 167.8, 155.7, 154.9, 154.5, 152.6, 134.4, 134.0,

129.0, 128.6, 128.6, 128.2, 128.1, 127.7, 127.4, 127.1, 126.9, 124.8, 124.1, 123.5, 123.0, 121.6, 113.9, 112.4, 111.6, 105.0, 101.0, 68.1, 60.8, 52.5, 51.7, 46.7, 46.0, 34.3, 33.8, 32.9, 28.1 **IR:** 2976 (w), 1774 (s), 1728 (m), 1514 (m) cm^{-1}. **HRMS (EI)** $[M+Na]^+$ m/z: Calcd. for $C_{21}H_{18}O_5Na$, 373.1046; found 373.1043.



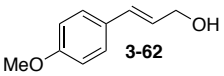
3-71

Methyl (1*S*,2*S*,3*R*)-2-(acetoxymethyl)-1-(benzofuran-2-carbonyl)-3-phenylcyclopropane-1-carboxylate: Cyclopropyl alcohol mixture **SI-3-1** (170 mg, <0.485 mmol) was dissolved in DCM (4.9 mL) and cooled to 0°C. Acetic anhydride (0.055 mL, 0.58 mmol), *N,N*-di(*iso*-propyl)ethylamine (0.10 mL, 0.58 mmol), and 4-(*N,N*-dimethylamino)pyridine (14 mg, 0.10 mmol) was added to the solution and stirred at 0°C for 1 hour. The reaction was quenched with 1% HCl, extracted three times with DCM, washed with water, dried over Na_2SO_4, filtered though celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.53, 30% EtOAc/Hexane) to give cyclopropyl acetate **3-71** (143 mg, <75% yield). **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.74 - 7.71 (m, 1 H), 7.60 - 7.56 (m, 2 H), 7.51 - 7.47 (m, 1 H), 7.35 - 7.24 (m, 6 H), 4.41 (dd, *J* = 6.1, 12.2 Hz, 1 H), 3.85 (dd, *J* = 8.9, 12.2 Hz, 1 H), 3.59 (d, *J* = 7.6 Hz, 1 H), 3.37 (s, 3 H), 3.23 (ddd, *J* = 6.4, 7.8, 9.0 Hz, 1 H), 1.69 (s, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 182.4, 170.4, 167.5, 155.6, 152.7, 133.7, 128.9, 128.5, 128.3, 127.5, 126.8, 124.1, 123.4, 113.4, 112.3, 61.7, 52.6, 46.2, 33.5, 30.4, 20.4. **IR:** 2951 (w), 1737 (s), 1670 (s), 1554 (s) cm^{-1}. **HRMS (ESI)** $[M+Na]^+$ m/z: Calcd. for $C_{23}H_{20}O_6Na$, 415.1152; found 415.1148.



***iso*-3-72**

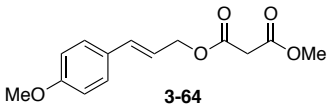
Methyl 4-(acetoxymethyl)-2-(benzofuran-2-yl)-5-phenyl-4,5-dihydrofuran-3-carboxylate: $Ca(NTf_2)_2$ (8 mg, 0.013 mmol) and *n*-Bu_4NPF_6 (5 mg, 0.013 mmol) was added to a flask. Compound **3-71** was dissolved in DCM (0.63 mL) and added to the catalyst mixture. The reaction was stirred for 3 hours and quenched with water. The aqueous layer was extracted three times with DCM, dried over Na_2SO_4, filtered through celite, and concentrated. The crude residue was purified by flash chromatography (R_f = 0.39, 20% EtOAc/Hexane) to give the title compound (21.5 mg, 43% yield). **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.32 (d, *J* = 0.9 Hz, 1 H), 7.72 - 7.67 (m, 1 H), 7.61 - 7.55 (m, 1 H), 7.44 - 7.37 (m, 4 H), 7.37 - 7.32 (m, 1 H), 7.32 - 7.27 (m, 1 H), 5.68 (d, *J* = 4.6 Hz, 1 H), 4.52 (dd, *J* = 3.7, 11.0 Hz, 1 H), 4.34 (dd, *J* = 7.9, 11.0 Hz, 1 H), 3.79 (s, 3 H), 3.73 - 3.67 (m, 1 H), 2.11 (s, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 170.9, 164.3, 156.4, 154.8, 144.8, 140.5, 128.8, 128.4, 127.8, 126.9, 125.1, 123.5, 122.5, 114.9, 111.8, 102.4, 85.8, 65.0, 52.0, 51.4, 20.9. **IR:** 1740 (s), 1701 (s), 1605 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{23}H_{20}O_6$, 392.1260; found 392.1250.



3-62

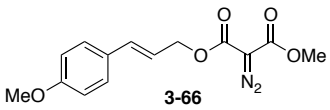
(*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol: Methyl (*E*)-3-(4-methoxyphenyl)acrylate (5.00 g, 26.0 mmol) was dissolved in DCM (50 mL) and cooled to -78°C. DIBAL-H (1M in DCM, 78 mL, 78 mmol) was added slowly and the reaction was stirred at -78°C for 2 hours. The reaction was quenched with sat. aq. Na_2SO_4 and aluminum salts filtered off. The filtrate was extracted three times with DCM, washed with brine, dried over $MgSO_4$,

filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.15, 20% EtOAc/Hexane) to give the title compound (3.81 g, 90% yield) as a white powder. All characterization was consistent with that previously reported.[26]



3-64

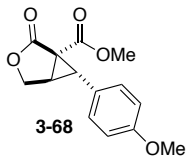
(*E*)-3-(4-methoxyphenyl)allyl methyl malonate: (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (3.80 g, 23.1 mmol) was dissolved in DCM (23 mL) and triethylamine (3.90 mL, 27.7 mmol) was added. The solution was cooled to 0°C and methyl malonyl chloride (2.75 mL, 25.5 mmol) was added slowly and warmed to room temperature overnight. The reaction was quenched with sat. aq. $NaHCO_3$, extracted three times with DCM, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.26, 20% EtOAc/Hexane) to give the title compound (5.38 g, 88% yield) as a colorless oil. Characterization was consistent with that reported.[27]



3-66

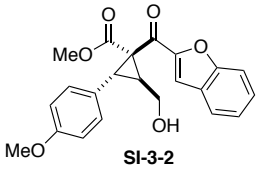
(*E*)-1-(3-(4-methoxyphenyl)allyl) 3-methyl 2-diazomalonate: (*E*)-3-(4-methoxyphenyl)allyl methyl malonate (3.45 g, 13.1 mmol) was dissolved in MeCN (26 mL) and triethylamine (2.20 mL, 15.8 mmol) was added and stirred for 10 minutes. Tosyl azide (2.40 mL, 15.7 mmol) was added and stirred at room temperature overnight. The reaction mixture was then concentrated. Tosyl amine byproduct was recrystallized with DCM and filtered. The filtrate was concentrated and purified by flash chromatography (R_f = 0.20, 20% EtOAc/Hexane) to give **3-66** (3.22 g, 85% yield) as a yellow oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.35 - 7.30 (m, 2 H), 6.88 - 6.84 (m, 2 H), 6.64 (d, *J* = 15.9 Hz, 1

H), 6.17 (td, *J* = 6.8, 15.8 Hz, 1 H), 4.87 (dd, *J* = 1.2, 6.7 Hz, 2 H), 3.84 (s, 3 H), 3.81 - 3.80 (m, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 161.6, 160.8, 159.7, 135.0, 128.7, 128.0, 127.1, 120.0, 114.0, 66.4, 55.3, 52.5. **IR:** 2955 (w), 2837 (w), 2135 (s), 1755 (s), 1732 (s), 1690 (m), 1607 (m), 1512 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{14}H_{14}O_5N_2$, 290.0903; found 290.0903.



3-68

Methyl (1*R*,5*S*,6*R*)-6-(4-methoxyphenyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate: $Rh_2(esp)_2$ (42 mg, 0.05 mmol) was dissolved in DCM (200 mL) and cooled to 0°C. Diazo **3-66** (3.20 g, 11.0 mmol) was dissolved in DCM (20 mL) and added all at once at 0°C. The reaction was warmed to room temperature overnight and quenched with sat. aq. thiourea, extracted three times with DCM, washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.14, 30% EtOAc/Hexane) to give the title compound (1.71 g, 59% yield) as a white solid. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.19 - 7.14 (m, 2 H), 6.86 - 6.82 (m, 1 H), 4.48 (dd, *J* = 4.9, 9.2 Hz, 1 H), 4.35 (d, *J* = 9.5 Hz, 1 H), 3.79 (s, 3 H), 3.54 (s, 3 H), 3.26 (t, *J* = 4.9 Hz, 1 H), 2.89 (d, *J* = 5.5 Hz, 1 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 170.1, 164.1, 159.4, 129.8, 123.4, 113.8, 67.2, 55.2, 52.7, 37.8, 37.5, 27.8. **IR:** 2955 (w), 1770 (s), 1726 (m), 1610 (m), 1516 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{14}H_{14}O_5$, 262.0841; found 262.0840.



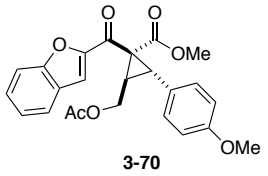
SI-3-2

: inseparable mixture of 2 unknown compounds

16.7 : 4.0 : 1

Methyl (1*S*,2*S*,3*R*)-1-(benzofuran-2-carbonyl)-2-(hydroxymethyl)-3-(4-methoxyphenyl)cyclopropane-1-carboxylate: Benzofuran (744 mg, 6.30 mmol) was dissolved in THF (2.8 mL) and cooled to 0°C. *n*-Butyllithium (1.7 M in hexane, 3.70 mL, 6.29 mmol) was added dropwise at 0°C and stirred for 30 minutes. The benzofuran solution was then warmed to room temperature and stirred 1 hour. The cyclopropyl lactone **3-68** (1.50 g, 5.72 mmol) was dissolved (with heating) in THF (45 mL) and cooled to 0°C. The benzofuran solution was then cannulated into the cyclopropyl lactone solution at 0°C and stirred for 2 hours. The reaction was quenched with sat. aq. NH_4Cl, extracted three times with EtOAc, washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.21, 30% EtOAc/Hexane) and the title compound was given as a mixture with other compounds (1.56 g, ratio: **16.7**:4.0:1) as an orange oil. The mixture was carried forward for acetylation. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.13 - 8.12 (m, 0.10 H), 7.75 - 7.71 (m, 1.00 H), 7.69 - 7.66 (m, 0.14 H), 7.64 - 7.60 (m, 1.20 H), 7.60 - 7.57 (m, 0.98 H), 7.57 - 7.53 (m, 0.39 H), 7.52 - 7.47 (m, 1.02 H), 7.41 - 7.37 (m, 0.17 H), 7.36 - 7.30 (m, 1.52 H), 7.30 - 7.24 (m, 3.04 H), 7.15 (dd, *J* = 0.6, 8.9 Hz, 0.51 H), 7.03 (d, *J* = 0.9 Hz, 0.22 H), 6.90 (d, *J* = 8.9 Hz, 0.28 H), 6.88 - 6.83 (m, 2.00 H), 6.81 (d, *J* = 8.9 Hz, 0.50 H), 5.66 - 5.63 (m, 0.12 H), 4.45 - 4.41 (m, 0.26 H), 4.18 (d, *J* = 8.5 Hz, 0.25 H), 3.99 - 3.93 (m, 1.38 H), 3.82 - 3.79 (m, 3.69 H), 3.78 (s, 0.73 H), 3.49 (dd, *J* = 8.9, 11.9 Hz, 1.03 H), 3.41 - 3.37 (m, 4.56 H), 3.12 - 3.04 (m, 1.28 H), 2.91 - 2.88 (m, 0.25 H), 1.90 - 1.79 (m,

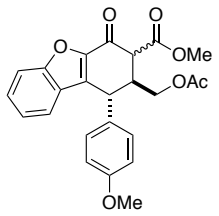
0.95 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 183.6, 168.3, 167.9, 158.9, 158.6, 155.7, 154.9, 154.6, 152.6, 145.2, 132.7, 130.0, 129.7, 128.6, 127.7, 127.0, 126.9, 126.8, 126.3, 125.9, 124.7, 124.1, 123.5, 123.4, 123.0, 122.4, 121.6, 114.3, 114.1, 113.9, 113.6, 113.6, 112.4, 111.8, 111.6, 104.9, 100.9, 85.9, 68.1, 64.3, 60.8, 55.3, 55.2, 54.9, 52.6, 51.8, 51.4, 46.6, 45.9, 34.6, 33.4, 32.5, 28.3. **IR:** 3464 (w), 2951 (w), 2837 (w), 1730 (m), 1667 (m), 1612 (m), 1552 (m), 1516 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{22}H_{20}O_6$, 380.1260; found 380.1260.



3-70

Methyl (1*S*,2*S*,3*R*)-2-(acetoxymethyl)-1-(benzofuran-2-carbonyl)-3-(4-methoxyphenyl)cyclopropane-1-carboxylate: The previous alcohol mixture **SI-3-7** (1.24 g) was dissolved in DCM (33 mL) and cooled to 0°C. Acetic anhydride (0.37 mL, 3.91 mmol), di(*iso*-propyl)ethylamine (0.68 mL, 3.91 mmol), and 4-(*N,N*-dimethylamino)pyridine (80 mg, 0.65 mmol) were added at 0°C and stirred for 1 hour. The reaction was quenched with 1% HCl, extracted three times with DCM, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.36, 30% EtOAc/Hexane) to give the title compound (1.29 g, 53% over 2 steps). **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.72 (td, *J* = 1.1, 7.9 Hz, 1 H), 7.59 - 7.56 (m, 2 H), 7.51 - 7.46 (m, 1 H), 7.32 (ddd, *J* = 0.9, 7.1, 7.9 Hz, 1 H), 7.24 - 7.19 (m, 2 H), 6.86 - 6.81 (m, 2 H), 4.41 (dd, *J* = 6.1, 12.2 Hz, 1 H), 3.82 (dd, *J* = 8.9, 12.2 Hz, 1 H), 3.79 (s, 3 H), 3.54 (d, *J* = 7.9 Hz, 1 H), 3.39 (s, 3 H), 3.18 (ddd, *J* = 6.0, 7.9, 9.1 Hz, 1 H), 1.68 (s, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 182.5, 170.4, 167.6, 158.9, 155.6,

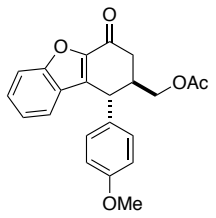
152.7, 129.9, 128.5, 126.8, 125.6, 124.1, 123.4, 113.7, 113.3, 112.3, 61.7, 55.2, 52.6, 46.2, 33.1, 30.7, 20.3. **IR:** 2953 (w), 1738 (s), 1670 (s), 1555 (s), 1516 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{24}H_{22}O_7$, 422.1366; found 422.1358.



3-73
dr = 4:0:1:0

Methyl (1*R*,2*S*)-2-(acetoxymethyl)-1-(4-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-3-carboxylate: Cyclopropane **3-70** (306 mg, 0.724 mmol) was dissolved in DCM (7.1 mL). $SnCl_4$ (25 μL, 0.21 mmol) was added and the mixture was stirred for 1 hour. The reaction was quenched with water, extracted three times with DCM, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.28, 30% EtOAc/Hexane) to give **3-73** (275 mg, 90% yield). *(Diastereomeric Ratio = 4.0:1:0)* **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.08 - 8.04 (m, 0.28 H), 7.61 - 7.53 (m, 1.38 H), 7.42 (ddd, *J* = 1.2, 7.1, 8.5 Hz, 1.36 H), 7.40 - 7.29 (m, 1.25 H), 7.19 - 7.15 (m, 2.27 H), 7.13 (d, *J* = 8.9 Hz, 0.76 H), 7.04 (ddd, *J* = 0.8, 7.1, 8.0 Hz, 1.44 H), 6.95 - 6.88 (m, 3.14 H), 6.64 - 6.61 (m, 0.26 H), 6.59 - 6.56 (m, 1.00 H), 4.70 - 4.66 (m, 0.27 H), 4.38 (d, *J* = 10.7 Hz, 1.34 H), 4.26 - 4.20 (m, 0.34 H), 4.09 - 4.01 (m, 1.66 H), 3.99 - 3.92 (m, 2.66 H), 3.88 (d, *J* = 12.2 Hz, 0.35 H), 3.85 - 3.82 (m, 8.32 H), 3.74 - 3.73 (m, 0.99 H), 3.16 - 3.08 (m, 1.31 H), 3.04 - 2.95 (m, 0.40 H), 2.13 - 2.10 (m, 3.63 H), 2.02 - 2.00 (m, 0.87 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 188.3, 182.3, 181.4, 170.4, 170.4, 170.4, 170.1, 169.7, 169.4, 168.1, 159.5, 159.4, 156.7, 155.2, 146.1,

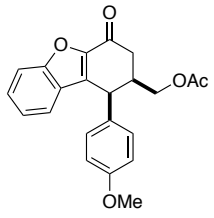
145.9, 137.8, 136.4, 130.9, 130.5, 129.9, 129.4, 129.4, 128.3, 128.1, 125.8, 125.7, 124.9, 123.7, 123.4, 123.2, 121.9, 114.6, 114.5, 112.8, 112.8, 111.5, 63.0, 62.5, 62.3, 56.9, 56.8, 55.3, 55.3, 55.3, 52.7, 52.6, 46.9, 46.3, 45.5, 42.5, 41.1, 40.0, 20.7, 20.6. **IR:** 1738 (s), 1674 (s), 1512 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{24}H_{22}O_7$, 422.1366; found 422.1364.



3-74

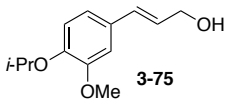
((1*R*,2*R*)-1-(4-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-2-yl)methyl acetate: Sodium chloride (64 mg, 1.13 mmol) was added to a flask with water (3 drops). The ß-ketoester **3-73** (160 mg, 0.379 mmol) was dissolved in DMSO (1.5 mL) and added. The mixture was heated to 150°C overnight and cooled to room temperature. The reaction was extracted three times with EtOAc, washed three times with brine, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.33, 30% EtOAc/Hexane) to give **3-74** (64 mg, 46% yield) as an orange oil. **^{1}H NMR** (800MHz, $CDCl_3$) δ = 7.54 - 7.52 (m, 1 H), 7.39 (ddd, *J* = 1.5, 7.2, 8.4 Hz, 1 H), 7.16 - 7.12 (m, 2 H), 7.03 (ddd, *J* = 1.0, 7.1, 8.1 Hz, 1 H), 6.91 - 6.87 (m, 2 H), 6.64 - 6.61 (m, 1 H), 4.27 - 4.23 (m, 1 H), 4.07 - 4.03 (m, 1 H), 4.03 - 3.99 (m, 1 H), 3.84 - 3.80 (m, 3 H), 2.90 - 2.85 (m, 1 H), 2.81 - 2.73 (m, 2 H), 2.06 (s, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 186.9, 170.7, 159.2, 156.3, 147.2, 135.9, 131.2, 129.6, 128.9, 125.9, 123.5, 123.0, 114.4, 112.7, 64.7, 55.3, 44.5, 42.3, 41.2, 20.7. **IR:** 2957 (w),

1736 (s), 1676 (s), 1512 (s) cm^{-1}. **HRMS (ESI)** $[M+H]^+$ m/z: Calcd. for $C_{22}H_{21}O_5$, 365.1384; found 365.1380.



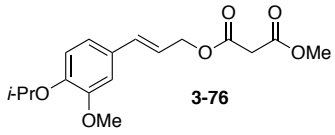
***epi*-3-74**

((1*S*,2*R*)-1-(4-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-2-yl)methyl acetate: Sodium chloride (64 mg, 1.13 mmol) was added to a flask with water (3 drops). The ß-ketoester **3-73** (160 mg, 0.379 mmol) was dissolved in DMSO (1.5 mL) and added. The mixture was heated to 150°C overnight and cooled to room temperature. The reaction was extracted three times with EtOAc, washed three times with brine, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.37, 30% EtOAc/Hexane) to give ***epi*-3-74** (10 mg, 7% yield) as a yellow oil. **^{1}H NMR** (800MHz, $CDCl_3$) δ = 8.13 (td, *J* = 0.7, 7.7 Hz, 1 H), 7.42 (td, *J* = 0.8, 8.1 Hz, 1 H), 7.37 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.35 - 7.32 (m, 1 H), 7.14 - 7.10 (m, 2 H), 6.96 - 6.91 (m, 2 H), 4.31 (d, *J* = 8.8 Hz, 1 H), 4.14 - 4.11 (m, 1 H), 4.09 - 4.05 (m, 1 H), 3.84 (s, 3 H), 2.85 (dd, *J* = 4.0, 16.3 Hz, 1 H), 2.82 - 2.76 (m, 1 H), 2.74 - 2.69 (m, 1 H), 2.09 (s, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 192.9, 170.7, 170.1, 159.3, 155.1, 129.5, 129.3, 125.4, 124.6, 121.9, 117.0, 114.5, 114.5, 111.4, 64.8, 55.3, 43.3, 43.2, 40.6, 20.8. **IR:** 1736 (s), 1672 (s), 1611 (m), 1584 (m), 1512 (s) cm^{-1}. **HRMS (ESI)** $[M+H]^+$ m/z: Calcd. for $C_{22}H_{21}O_5$, 365.1384; found 365.1384.



3-75

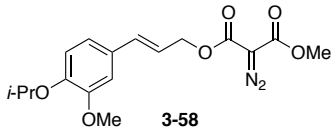
(*E*)-3-(4-isopropoxy-3-methoxyphenyl)prop-2-en-1-ol: Methyl (*E*)-3-(4-isopropoxy-3-methoxyphenyl) acrylate[7] (3.00 g, 12.0 mmol) was dissolved in DCM (30 mL) and cooled to -78°C. DIBAL-H (1 M in DCM, 36 mL, 36 mmol) was added dropwise and the reaction was stirred at -78°C for 1 hour. The reaction was quenched with sat. aq. Na_2SO_4 and the aluminum salts filtered off. The filtrate was extracted three times with DCM, dried over $MgSO_4$, filtered through celite, and concentrated to give the title compound (2.71 g, >99% yield) as a cloudy oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 6.94 (d, *J* = 2.1 Hz, 1 H), 6.89 (dd, *J* = 2.1, 8.2 Hz, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 6.54 (td, *J* = 1.4, 15.9 Hz, 1 H), 6.24 (td, *J* = 6.0, 15.9 Hz, 1 H), 4.52 (spt, *J* = 6.1 Hz, 1 H), 4.30 (dt, *J* = 1.4, 5.9 Hz, 2 H), 3.86 (s, 3 H), 1.50 (br. s., 1 H), 1.38 - 1.34 (m, 6 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 150.3, 147.2, 131.2, 130.0, 126.5, 119.5, 115.5, 109.6, 71.4, 63.8, 55.9, 22.0. **IR:** 3381 (br., w), 2976 (w), 2934 (w), 1508 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{13}H_{18}O_3$, 222.1256; found 222.1255.



3-76

(*E*)-3-(4-isopropoxy-3-methoxyphenyl)allyl methyl malonate: Alcohol **3-75** (2.01 g, 9.00 mmol) was dissolved in DCM (9 mL), triethylamine (1.50 mL, 10.8 mmol) was added, and the solution was cooled to 0°C. Methyl malonyl chloride (1.1 mL, 10.2 mmol) was added slowly and warmed to room temperature overnight. The reaction was quenched with sat. aq. $NaHCO_3$, extracted three times with DCM, dried over $MgSO_4$, filtered though celite, and concentrated to give the title compound (2.75 g, 94% yield) as

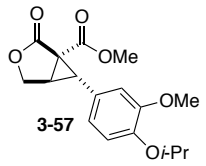
a pale yellow oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 6.93 (d, *J* = 2.1 Hz, 1 H), 6.91 - 6.88 (m, 1 H), 6.85 - 6.81 (m, 1 H), 6.60 (d, *J* = 15.9 Hz, 1 H), 6.14 (td, *J* = 6.7, 15.9 Hz, 1 H), 4.78 (dd, *J* = 1.2, 6.7 Hz, 2 H), 4.53 (spt, *J* = 6.1 Hz, 1 H), 3.86 (s, 3 H), 3.75 (s, 3 H), 3.42 (s, 2 H), 1.36 (d, *J* = 6.1 Hz, 6 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 166.9, 166.3, 150.3, 147.6, 135.0, 129.2, 120.2, 119.9, 115.2, 109.6, 71.3, 66.3, 55.9, 52.5, 41.3, 22.0. **IR:** 2976 (w), 1732 (s), 1508 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{17}H_{22}O_6$, 322.1416; found 322.1402.



3-58

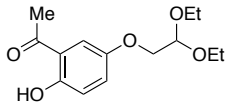
(*E*)-1-(3-(4-isopropoxy-3-methoxyphenyl)allyl) 3-methyl 2-diazomalonate: Compound **3-76** (2.00 g, 6.20 mmol) was dissolved in MeCN (31 mL) and triethylamine (1.05 mL, 7.45 mmol) was added and stirred for 10 minutes. Tosyl azide (1.15 mL, 7.45 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was then concentrated. The tosyl amine byproduct was recrystallized with DCM and filtered. The filtrate was concentrated and purified by flash chromatography (R_f = 0.54, 50% EtOAc/Hexane) to give the title compound (1.52 g, 70% yield) as a yellow oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 6.94 (d, *J* = 1.8 Hz, 1 H), 6.90 (dd, *J* = 1.8, 8.2 Hz, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 6.63 (d, *J* = 15.6 Hz, 1 H), 6.18 (td, *J* = 6.7, 15.9 Hz, 1 H), 4.87 (dd, *J* = 1.2, 6.7 Hz, 2 H), 4.54 (spt, *J* = 6.1 Hz, 1 H), 3.87 (s, 2 H), 3.85 (s, 3 H), 1.37 (d, *J* = 6.1 Hz, 6 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 161.5, 160.8, 150.3, 147.7, 135.4, 129.2, 120.3, 120.1, 115.3, 109.6, 71.3, 66.4, 55.9, 52.5, 22.0. **IR:** 2976 (w), 2137 (s),

1757 (s), 1735 (s), 1691 (m), 1510 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{17}H_{20}O_6N_2$, 348.1321; found 348.1315.



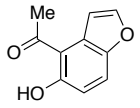
3-57

Methyl (1*R*,5*S*,6*R*)-6-(4-isopropoxy-3-methoxyphenyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate: $Rh_2(esp)_2$ (16 mg, 0.02 mmol) was added to a flask and dissolved in DCM (150 mL) and cooled to 0°C. Diazo **3-58** (1.50 g, 4.30 mmol) was dissolved in DCM (50 mL) and added in one portion at 0°C and warmed to room temperature overnight. The reaction was quenched with sat. aq. thiourea, extracted three times with DCM, washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.31, 50% EtOAc/Hexane) to give the cyclopropyl lactone **3-57** (811 mg, 59% yield) as a pale yellow solid. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 6.81 (d, *J* = 8.2 Hz, 1 H), 6.76 (d, *J* = 1.8 Hz, 1 H), 6.74 (ddd, *J* = 0.6, 2.1, 7.9 Hz, 1 H), 4.55 - 4.45 (m, 2 H), 4.37 - 4.32 (m, 1 H), 3.82 (s, 3 H), 3.54 (s, 3 H), 3.26 - 3.23 (m, 1 H), 2.87 (d, *J* = 5.5 Hz, 1 H), 1.34 (dd, *J* = 1.2, 6.1 Hz, 6 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 170.1, 164.0, 150.0, 147.2, 124.2, 120.7, 114.9, 112.4, 71.2, 67.3, 56.0, 52.6, 37.9, 37.7, 27.7, 22.0, 21.9. **IR:** 2984 (w), 2913 (w), 1770 (s), 1730 (s), 1516 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{17}H_{20}O_6$, 320.1260; found 320.1259.



3-79

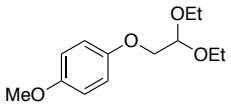
1-(5-(2,2-diethoxyethoxy)-2-hydroxyphenyl)ethan-1-one: Prepared according to previously published conditions.[21] Potassium carbonate (454 mg, 3.29 mmol) and 2', 5'-dihydroxyacetophenone (500 mg, 3.29 mmol) were combined and suspended in DMF (4 mL). The suspension was heated to reflux and bromoacetaldehyde diethyl acetal (0.50 mL, 3.29 mmol) in DMF (4 mL) was added via syringe pump over 1 hour. The reaction stirred for 4 hours at reflux and then cooled to room temperature. The reaction was quenched with water, extracted three times with EtOAc, washed three times with brine, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.52, 20% EtOAc/Hexane) to give the acetal **3-79** (200 mg, 23% yield) as a yellow oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 11.86 (s, 1 H), 7.23 (d, *J* = 3.1 Hz, 1 H), 7.14 (dd, *J* = 3.1, 9.2 Hz, 1 H), 6.91 (d, *J* = 9.2 Hz, 1 H), 4.82 (t, *J* = 5.2 Hz, 1 H), 3.98 (d, *J* = 5.2 Hz, 2 H), 3.77 (qd, *J* = 7.0, 9.4 Hz, 2 H), 3.64 (qd, *J* = 7.1, 9.3 Hz, 2 H), 2.60 (s, 3 H), 1.25 (t, *J* = 7.0 Hz, 6 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 204.0, 157.0, 150.7, 124.9, 119.2, 119.2, 114.8, 100.5, 69.5, 62.7, 26.8, 15.3. **IR:** 2976 (w), 2932 (w), 2882 (w), 1645 (m), 1618 (m), 1483 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{14}H_{20}O_5$, 268.1311; found 268.1314.



3-81

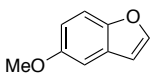
1-(5-hydroxybenzofuran-4-yl)ethan-1-one: Acetal **3-79** (502 mg, 1.87 mmol) was dissolved in toluene (9.3 mL) and added to Amberlyst 15 (~50 mg) and heated to reflux overnight using a Dean-Stark apparatus for subsequent removal of water. The reaction

was filtered through celite and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.64, 30% EtOAc/Hex) to give **3-81** (67 mg, 20% yield) as a yellow oil**.** **^{1}H NMR** (500MHz, $CDCl_3$) δ = 13.00 (s, 1 H), 7.74 - 7.73 (m, 1 H), 7.61 (dd, *J* = 1.1, 9.0 Hz, 1 H), 6.95 (dd, *J* = 0.9, 2.1 Hz, 1 H), 6.93 - 6.89 (m, 1 H), 2.76 (s, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 203.3, 161.2, 148.7, 147.0, 126.3, 119.9, 115.3, 111.8, 107.5, 31.1. **IR:** 3130 (w), 2965 (w), 1608 (s), 1481 (s), 1421 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{10}H_8O_3$, 176.0473; found 176.0474.



3-83

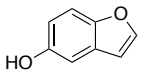
1-(2,2-diethoxyethoxy)-4-methoxybenzene: 4-hydroxyanisole (5.05 g, 40.7 mmol) and K_2CO_3 (5.55g, 40.7 mmol) were dissolved in DMF (100 mL) and bromoacetaldehyde diethyl acetal (6.05 mL, 40.7 mmol) was added. The mixture was heated to reflux overnight, cooled to room temperature, quenched with water, extracted three times with DCM, washed three times with brine, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.82, 30% EtOAc/Hexane) to give the acetal **3-83** (6.24 g, 57% yield) as a pale yellow oil. Characterization was consistent with that reported.[28]



3-84

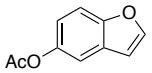
5-methoxybenzofuran: Acetal **3-83** (199 mg, 0.75 mmol) was dissolved in toluene (2 mL) and added to Amberlyst 15 (~20 mg) and heated to reflux overnight using a Dean-Stark apparatus for subsequent removal of water. The reaction was filtered through celite

and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.57, 10% EtOAc/Hex) to give **3-84** (85 mg, 77% yield) as a pale brown solid. Characterization was consistent with that reported.[28]



3-85

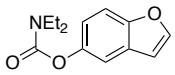
Benzofuran-5-ol: Prepared according to a previously published procedure.[29] 5-methoxybenzofuran (203 mg, 1.37 mmol) was dissolved in DCM (2 mL) and cooled to -78°C. Boron tribromide (1 M solution in DCM, 1.75 mL, 1.75 mmol) was added slowly and stirred for 2 hours at -78°C, warmed and stirred at room temperature for 1 hour, and quenched with 1 M HCl. The mixture was extracted three times with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.29, 20% EtOAc/Hexane) to give the title compound (137 mg, 74% yield) as a white solid. Characterization was consistent with that reported.



3-86

Benzofuran-5-yl acetate: Benzofuran-5-ol (112 mg, 0.835 mmol) was dissolved in DCM and cooled to 0°C. Acetic anhydride (0.09 mL, 1.00 mmol), diisopropylethyl amine (0.17 mL, 1.00 mmol), and 4-(*N,N*-dimethylamino)pyridine (20 mg, 0.17 mmol) was added and stirred for 30 minutes at 0°C. The reaction was quenched with 1% HCl, extracted three times with DCM, washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.50, 20% EtOAc/Hexane) to give the title compound (121 mg, 82% yield) as a white solid. **^{1}H NMR** (500MHz, $CDCl_3$) d = 7.65 (d, *J* = 2.1 Hz, 1 H), 7.48 (d, *J* = 8.9 Hz, 1

H), 7.33 - 7.30 (m, 1 H), 7.03 - 6.98 (m, 1 H), 6.76 (dd, *J* = 0.9, 2.1 Hz, 1 H), 2.33 (s, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) d = 170.0, 152.5, 146.3, 128.1, 118.1, 113.7, 111.8, 106.8, 21.1. **IR:** 3157 (w), 3132 (w), 3067 (w), 2920 (w), 1753 (m), 1622 (s), 1485 (s), 1423 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{10}H_8O_3$, 176.0473; found 176.0471.



3-87

Benzofuran-5-yl diethylcarbamate: Synthesized according to a Chein's protocol.[23] Benzofuran-5-ol (485 mg, 3.62 mmol) was dissolved in MeCN (7.2 mL) and K_2CO_3 (750 mg, 5.42 mmol) and diethyl carbamoyl chloride (0.69 mL, 5.42 mmol) were added. The mixture was heated to reflux for 18 hours, cooled, and quenched with water. The aqueous layer was extracted three times with EtOAc, dried over Na_2SO_4, filtered through celite, and concentrated. The crude residue was purified by flash chromatography (R_f = 0.20, 10% EtOAc/Hexane) to give the title compound (857 mg, >99% yield). **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.62 (d, *J* = 2.1 Hz, 1 H), 7.48 - 7.43 (m, 1 H), 7.34 (d, *J* = 2.4 Hz, 1 H), 7.04 (dd, *J* = 2.3, 8.7 Hz, 1 H), 6.73 (dd, *J* = 1.1, 2.3 Hz, 1 H), 3.52 - 3.35 (m, 4 H), 1.32 - 1.17 (m, 6 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 154.7, 152.2, 147.1, 146.0, 127.9, 118.5, 113.9, 111.5, 106.8, 42.2, 41.8, 14.2, 13.4. **IR:** 1708 (s) cm^{-1}. **HRMS (ESI)** $[M+Na]^+$ m/z: Calcd. for $C_{13}H_{15}NO_3Na$, 256.0944; found 256.0945.

3.6.2 NMR Spectra

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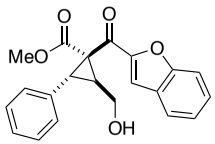


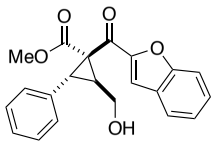
: unknown byproduct

SI-3-1 3.8 : 1

Acquisition Time (sec)	1.1010	***Comment***	5 mm PABBO BB/19F-1H/D Z-GRD Z113652/0157			***Date***	13 Oct 2015 10:53:52
Date Stamp	13 Oct 2015 10:53:52			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-II-94B-T3\3\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	257	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12571.1523	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.127

CWW-II-94B-T3-13C.esp

VerticalScaleFactor = 1



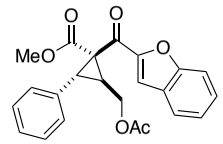
: unknown byproduct

SI-3-1 3.8 : 1

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	26 Apr 2017 13:33:52
Date Stamp	26 Apr 2017 13:33:52			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-43B\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	62.07	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.3035	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.001

CWW-III-43B-1H.esp

VerticalScaleFactor = 1

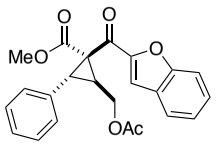


3-71

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	26 Apr 2017 13:38:08
Date Stamp	26 Apr 2017 13:38:08			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-43B\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	48	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.9688	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.001

CWW-III-43B-13C.esp

VerticalScaleFactor = 1

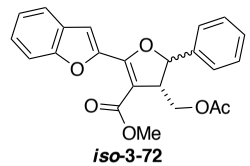


3-71

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	18 Aug 2016 13:50:56
Date Stamp	18 Aug 2016 13:50:56			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-44B-T1\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	29.88	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.9980	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.002

CWW-III-44B-T1-1H.esp

VerticalScaleFactor = 1



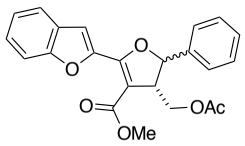
***iso*-3-72**

5/26/2018 12:01:47 AM

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	18 Aug 2016 13:59:28
Date Stamp	18 Aug 2016 13:59:28			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-44B-T1\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	64	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.0615	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.998

CWW-III-44B-T1.002.esp

VerticalScaleFactor = 1

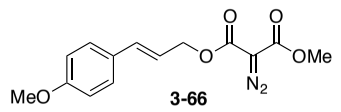


***iso*-3-72**

Acquisition Time (sec)	3.5504	***Comment***	Std Proton parameters			***Date***	Dec 7 2016
Date Stamp	Dec 7 2016	***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-76B-1H.fid\fid				
Frequency (MHz)	300.22	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	17053
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1801.9293	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4803.07	***Temperature (degree C)***	AMBIENT TEMPERATURE

CWW-III-76B-1H.esp

VerticalScaleFactor = 1

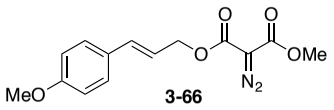


3-66

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	26 Apr 2017 13:25:20
Date Stamp	26 Apr 2017 13:25:20			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-76B\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	48	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12573.8770	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.000

CWW-III-76B-13C.esp

VerticalScaleFactor = 1

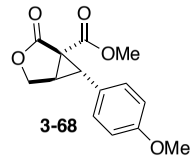


3-66

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	12 Dec 2016 10:13:04
Date Stamp	12 Dec 2016 10:13:04			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-78A\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	54.49	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.6931	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.000

CWW-III-78A-1H.esp

VerticalScaleFactor = 1

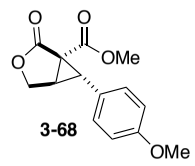


3-68

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	12 Dec 2016 10:28:00
Date Stamp	12 Dec 2016 10:28:00			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-78A\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	32	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.0605	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.001

CWW-III-78A-13C.esp

VerticalScaleFactor = 1

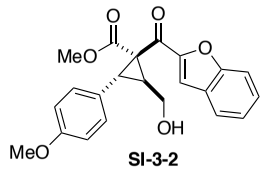


3-68

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	28 Apr 2017 17:09:20
Date Stamp	28 Apr 2017 17:09:20			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-79A-T41\2\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	54.49	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.6084	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.001

CWW-III-79A-T41-1H.esp

VerticalScaleFactor = 1



SI-3-2

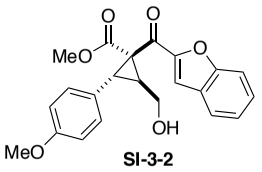
: inseparable mixture of 2 unknown compounds

16.7 : 4.0 : 1

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	28 Apr 2017 17:13:36
Date Stamp	28 Apr 2017 17:13:36			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-79A-T41\3\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	199	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.9688	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.998

CWW-III-79A-T41-13C.esp

VerticalScaleFactor = 1



SI-3-2

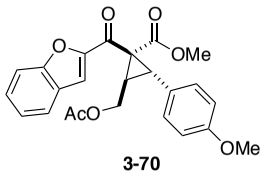
: inseparable mixture of 2 unknown compounds

16.7 : 4.0 : 1

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	11 Jan 2017 09:32:32
Date Stamp	11 Jan 2017 09:32:32			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-80A\3\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	29.88	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.6084	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.000

CWW-III-80A-1H.esp

VerticalScaleFactor = 1

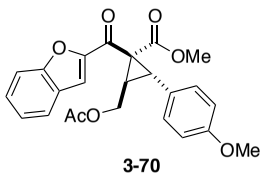


3-70

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	11 Jan 2017 09:38:56
Date Stamp	11 Jan 2017 09:38:56			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-80A\4\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	64	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.0625	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.997

CWW-III-80A-13C.esp

VerticalScaleFactor = 1

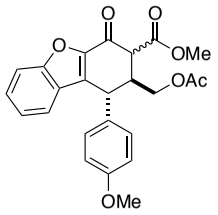


3-70

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	27 Apr 2017 11:15:12
Date Stamp	27 Apr 2017 11:15:12			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-90B\3\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	29.88	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.3035	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.961

CWW-III-90B-1H.esp

VerticalScaleFactor = 1

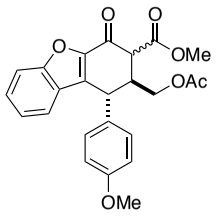


3-73
dr = 4:0:1:0

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	27 Apr 2017 11:19:28
Date Stamp	27 Apr 2017 11:19:28			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-90B\4\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	252	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.9707	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.001

CWW-III-90B-13C.esp

VerticalScaleFactor = 1

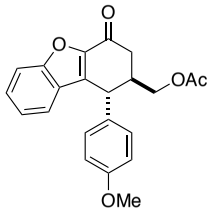


3-73
dr = 4:0:1:0

Acquisition Time (sec)	2.0447	***Comment***	Z123665_0002 (CP QCI 800S4 H-P/C/N-D-05 Z LT)			***Date***	23 Jan 2017 15:35:12
Date Stamp	23 Jan 2017 15:35:12			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T3-800\1\fid		
Frequency (MHz)	800.23	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	8.05	***SW(cyclical) (Hz)***	16025.64	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4941.4229	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	16025.15	***Temperature (degree C)***	24.997

REM-I-17A-T3-800-1H.esp

VerticalScaleFactor = 1



3-74

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	18 Jan 2017 14:48:16
Date Stamp	18 Jan 2017 14:48:16			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T3\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	32	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12569.7842	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.999

REM-I-17A-T3-13C.esp

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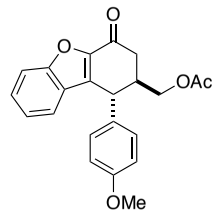
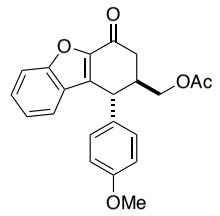


3-74

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	19 Jan 2017 10:04:32
Date Stamp	19 Jan 2017 10:04:32			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T3\8\PDATA\1\1r		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	41	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	dept135
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12554.8564	***Spectrum Type***	DEPT135	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.001

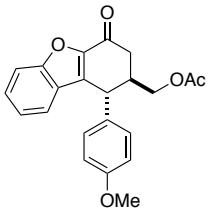
REM-I-17A-T3-DEPT.esp

VerticalScaleFactor = 1



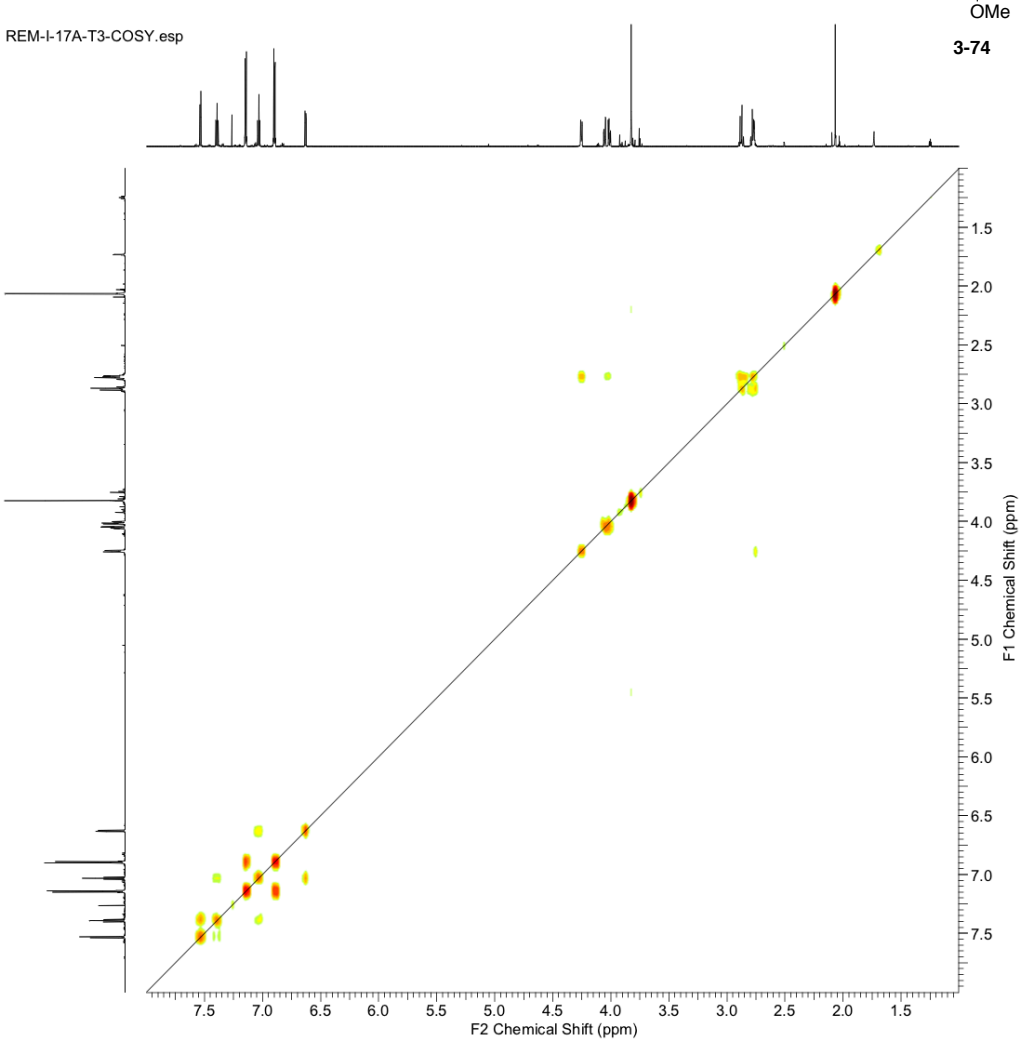
3-74

Acquisition Time (sec)	(0.4817, 0.0301)	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039
Date	19 Jan 2017 18:39:40		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T3\3\PDATA\1\2rr		
Frequency (MHz)	(500.27, 500.27)	***Nucleus***	(1H, 1H)
Number of Transients	1	***Origin***	spect
Original Points Count	(2048, 128)	***Owner***	cwilliam
Points Count	(1024, 1024)	***Pulse Sequence***	cosygpqf
Solvent	CDCl3	***Spectrum Type***	COSY
Sweep Width (Hz)	(4247.55, 4247.55)	***Temperature (degree C)***	25.001

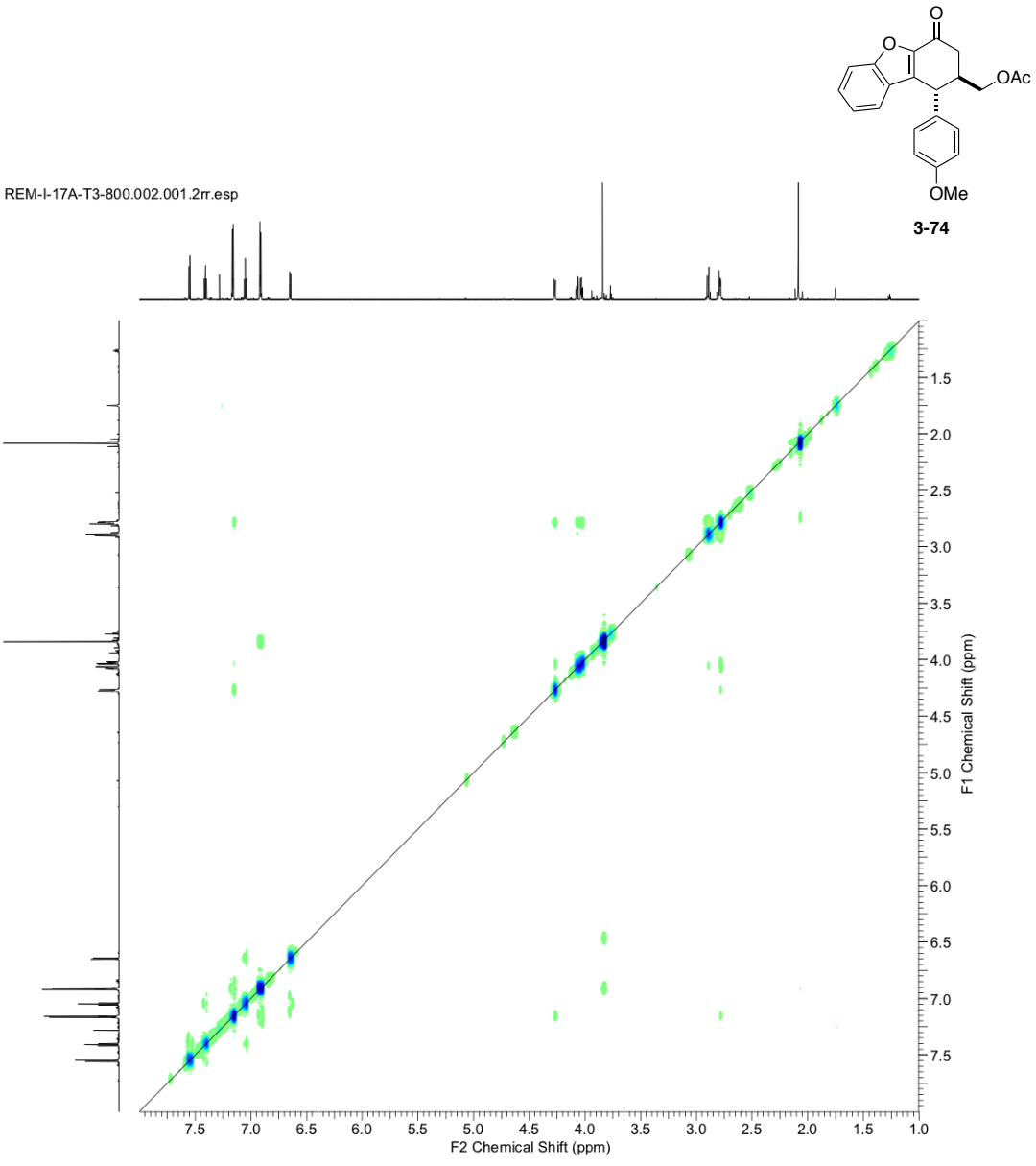


3-74

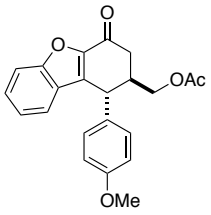
REM-I-17A-T3-COSY.esp



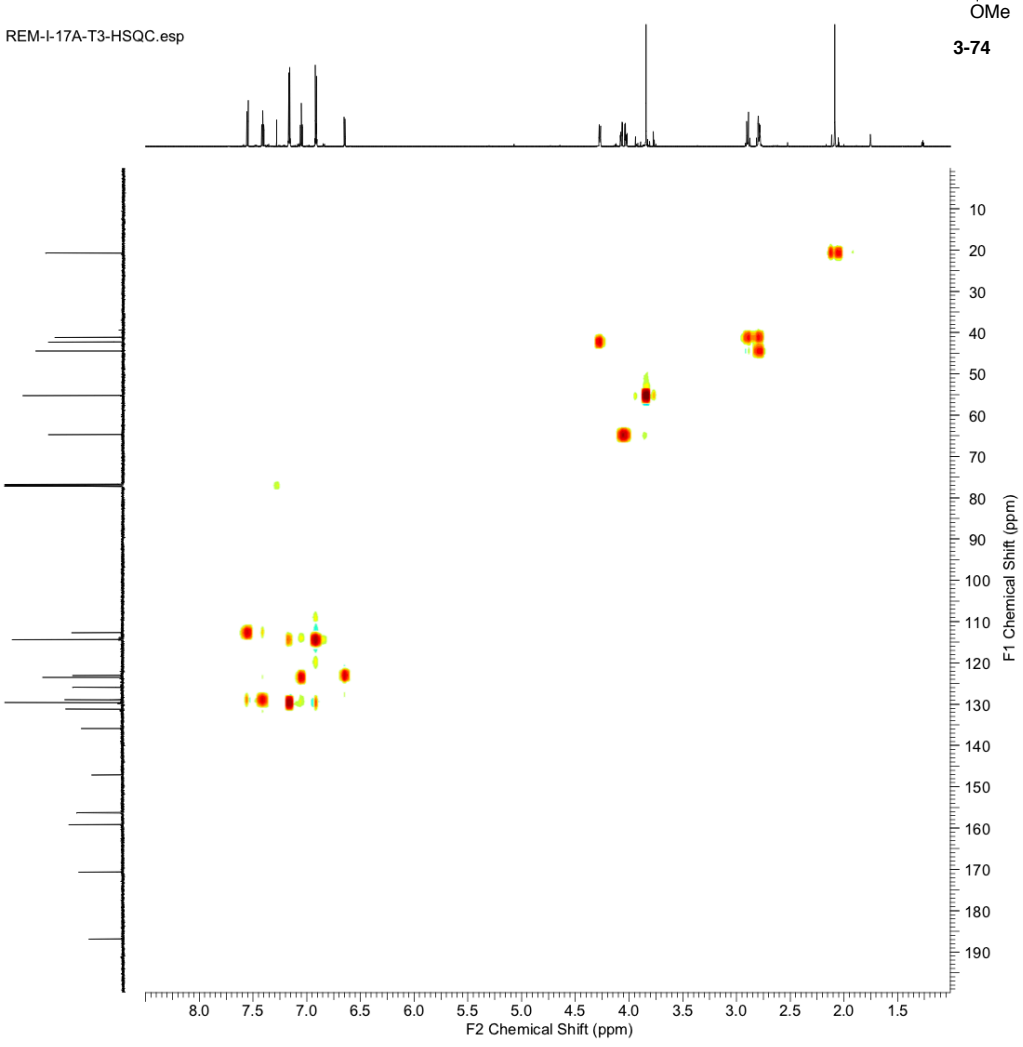
Acquisition Time (sec)	(0.1420, 0.0355)	***Comment***	Z123665_0002 (CP QCI 800S4 H-P/C/N-D-05 Z LT)
Date	24 Jan 2017 14:41:18		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T3-800\2\PDATA\1\2rr		
Frequency (MHz)	(800.23, 800.23)	***Nucleus***	(1H, 1H)
Number of Transients	4	***Origin***	spect
Original Points Count	(1024, 256)	***Owner***	cwilliam
Points Count	(1024, 1024)	***Pulse Sequence***	noesygpphpp
Solvent	CDCl3	***Spectrum Type***	NOESY
Sweep Width (Hz)	(7204.50, 7207.96)	***Temperature (degree C)***	25.002



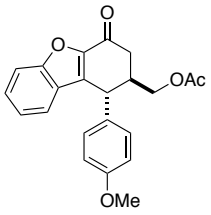
Acquisition Time (sec)	(0.1364, 0.0051)	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039
Date	19 Jan 2017 18:39:36		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T3\9\PDATA\1\2rr		
Frequency (MHz)	(500.27, 125.81)	***Nucleus***	(1H, 13C)
Number of Transients	2	***Origin***	spect
Original Points Count	(512, 128)	***Owner***	cwilliam
Points Count	(1024, 1024)	***Pulse Sequence***	hsqcetgpsi2
Solvent	CDCl3	***Spectrum Type***	HSQC
Sweep Width (Hz)	(3750.09, 25101.09)	***Temperature (degree C)***	25.002



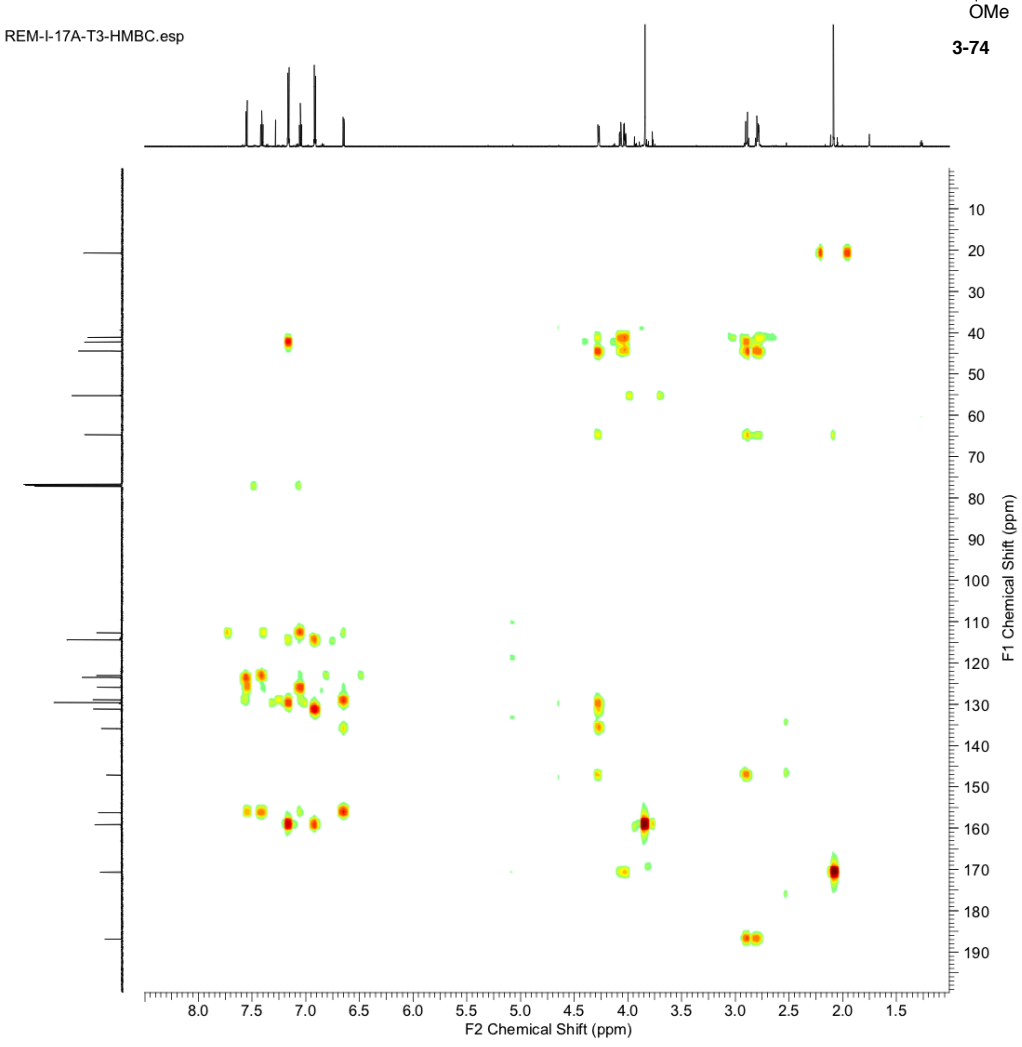
3-74



Acquisition Time (sec)	(0.2728, 0.0051)	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039
Date	19 Jan 2017 18:39:40		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T3\10\PDATA\1\2rr		
Frequency (MHz)	(500.27, 125.81)	***Nucleus***	(1H, 13C)
Number of Transients	4	***Origin***	spect
Original Points Count	(1024, 128)	***Owner***	cwilliam
Points Count	(2048, 1024)	***Pulse Sequence***	hmbcgplpndqf
Solvent	CDCl3	***Spectrum Type***	HMBC
Sweep Width (Hz)	(3751.92, 25101.09)	***Temperature (degree C)***	25.001



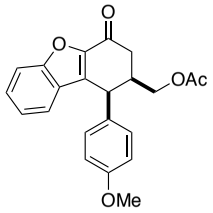
3-74



Acquisition Time (sec)	2.0447	***Comment***	Z123665_0002 (CP QCI 800S4 H-P/C/N-D-05 Z LT)			***Date***	24 Jan 2017 15:13:52
Date Stamp	24 Jan 2017 15:13:52			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T2-800\1\PDATA\1\1r		
Frequency (MHz)	800.23	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	6.40	***SW(cyclical) (Hz)***	16025.64	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4941.4229	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	16025.40	***Temperature (degree C)***	25.001

REM-I-17A-T2-800-1H.esp

VerticalScaleFactor = 1

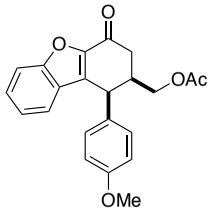


***epi*-3-74**

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	18 Jan 2017 13:27:12
Date Stamp	18 Jan 2017 13:27:12			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T2\2\PDATA\1\1r		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	96	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12573.8779	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.999

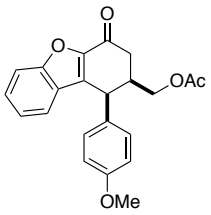
REM-I-17A-T2-13C.esp

VerticalScaleFactor = 1

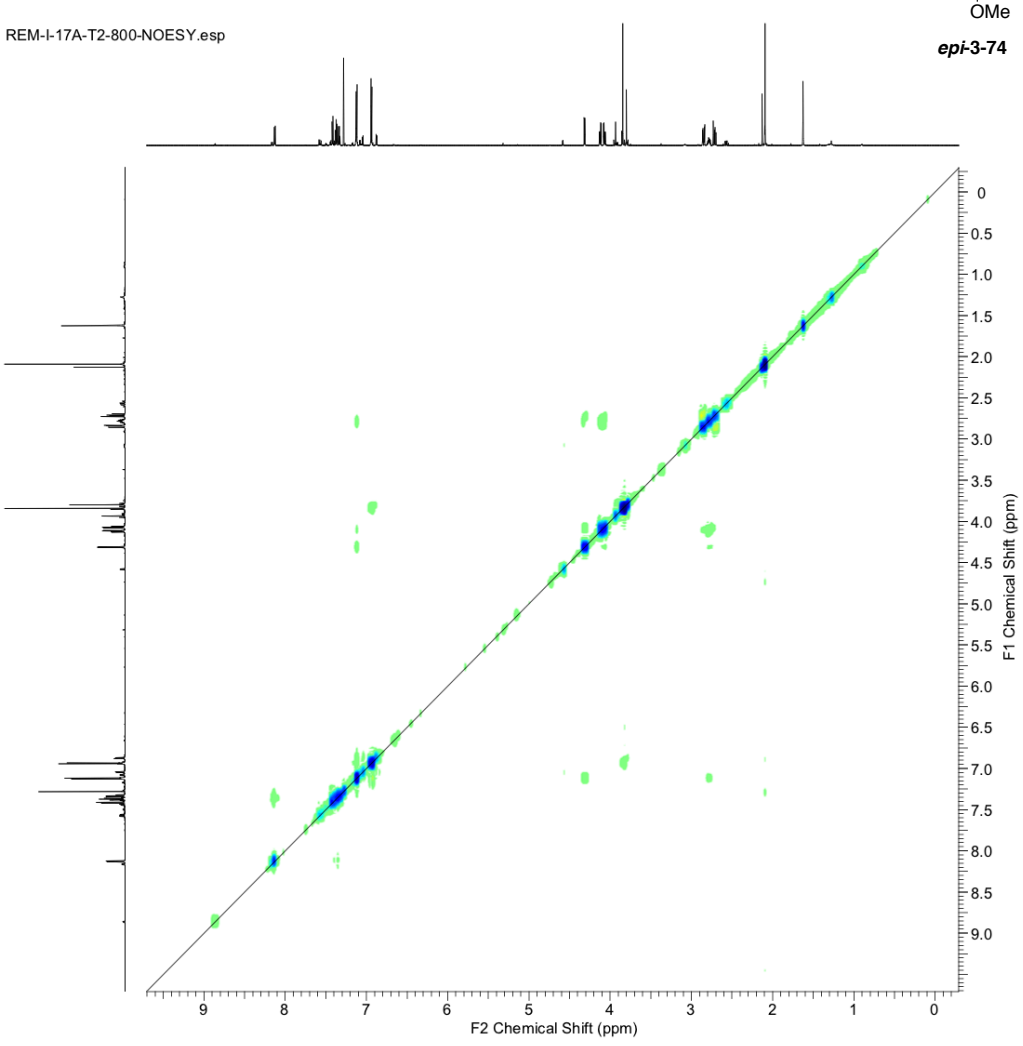


***epi*-3-74**

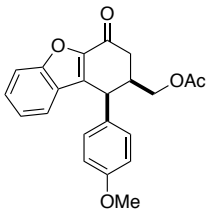
Acquisition Time (sec)	(0.1278, 0.0319)	***Comment***	Z123665_0002 (CP QCI 800S4 H-P/C/N-D-05 Z LT)
Date	26 Jan 2017 18:56:06		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T2-800\2\PDATA\1\2rr		
Frequency (MHz)	(800.23, 800.23)	***Nucleus***	(1H, 1H)
Number of Transients	4	***Origin***	spect
Original Points Count	(1024, 256)	***Owner***	cwilliam
Points Count	(1024, 1024)	***Pulse Sequence***	noesygpphpp
Solvent	CDCl3	***Spectrum Type***	NOESY
Sweep Width (Hz)	(8005.00, 8005.00)	***Temperature (degree C)***	25.002



***epi*-3-74**

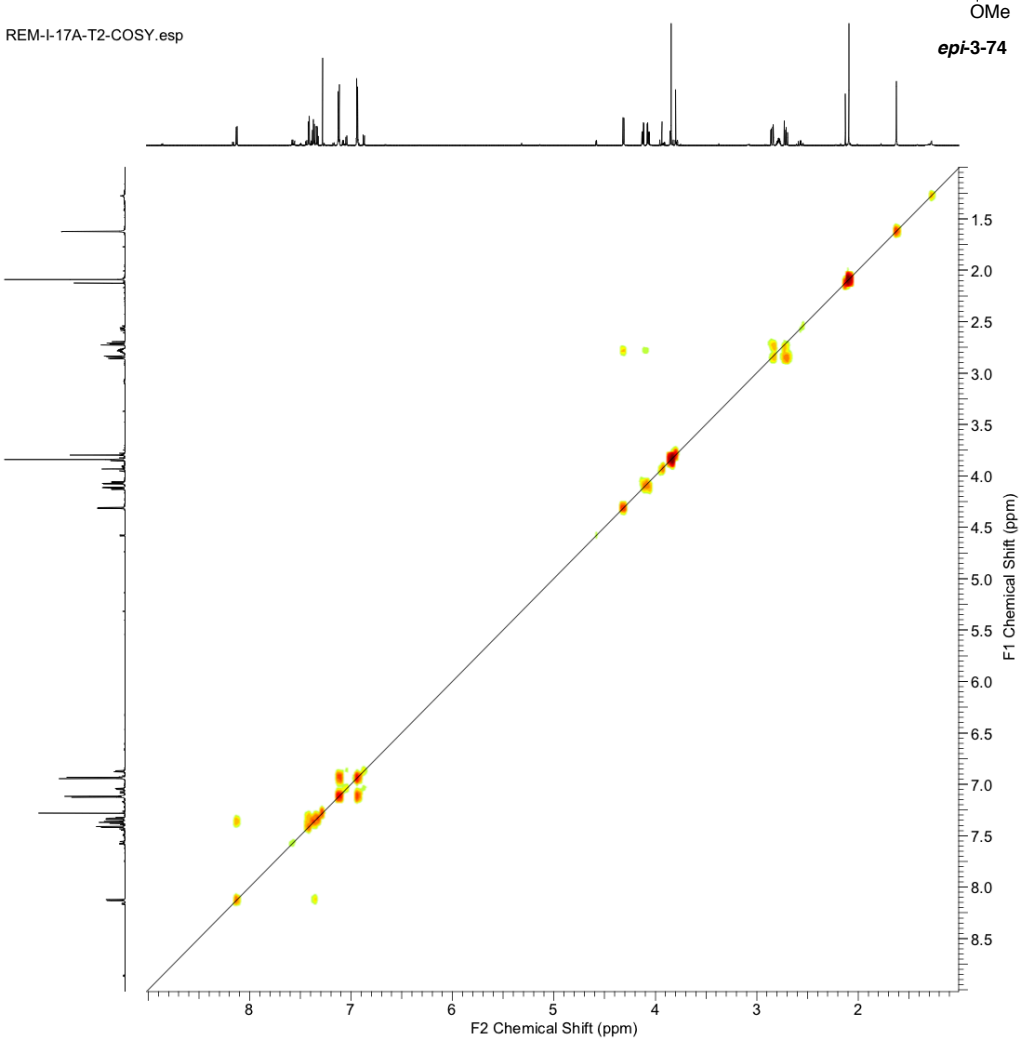


Acquisition Time (sec)	(0.5104, 0.0319)	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039
Date	19 Jan 2017 18:39:32		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T2\3\PDATA\1\2rr		
Frequency (MHz)	(500.27, 500.27)	***Nucleus***	(1H, 1H)
Number of Transients	1	***Origin***	spect
Original Points Count	(2048, 128)	***Owner***	cwilliam
Points Count	(1024, 1024)	***Pulse Sequence***	cosygpqf
Solvent	CDCl3	***Spectrum Type***	COSY
Sweep Width (Hz)	(4008.92, 4008.92)	***Temperature (degree C)***	24.999

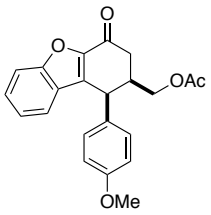


***epi*-3-74**

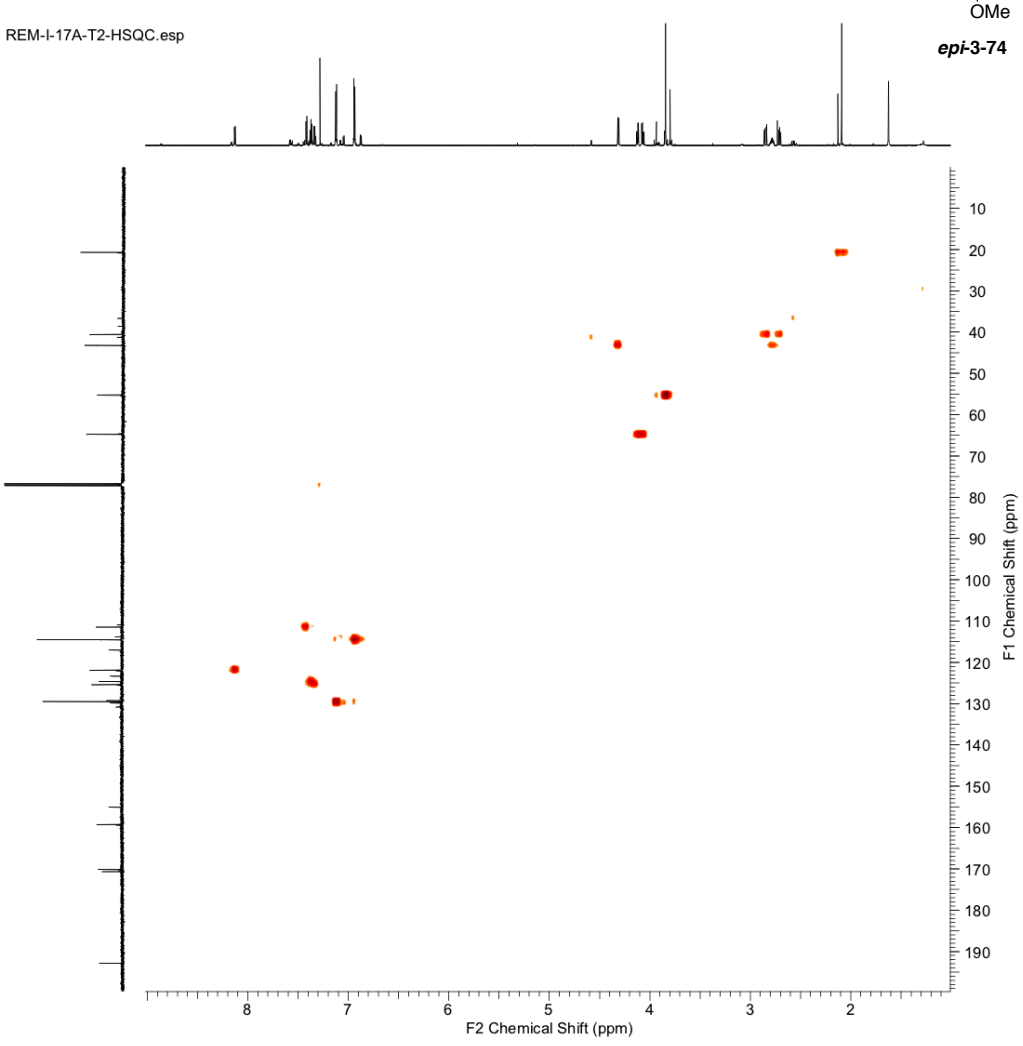
REM-I-17A-T2-COSY.esp



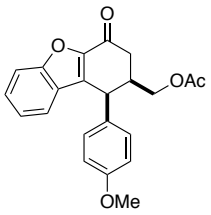
Acquisition Time (sec)	(0.1276, 0.0102)	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039
Date	19 Jan 2017 18:39:34		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T2\4\PDATA\1\2rr		
Frequency (MHz)	(500.27, 125.81)	***Nucleus***	(1H, 13C)
Number of Transients	2	***Origin***	spect
Original Points Count	(512, 256)	***Owner***	cwilliam
Points Count	(1024, 1024)	***Pulse Sequence***	hsqcetgpsi2
Solvent	CDCl3	***Spectrum Type***	HSQC
Sweep Width (Hz)	(4008.92, 25101.09)	***Temperature (degree C)***	24.999



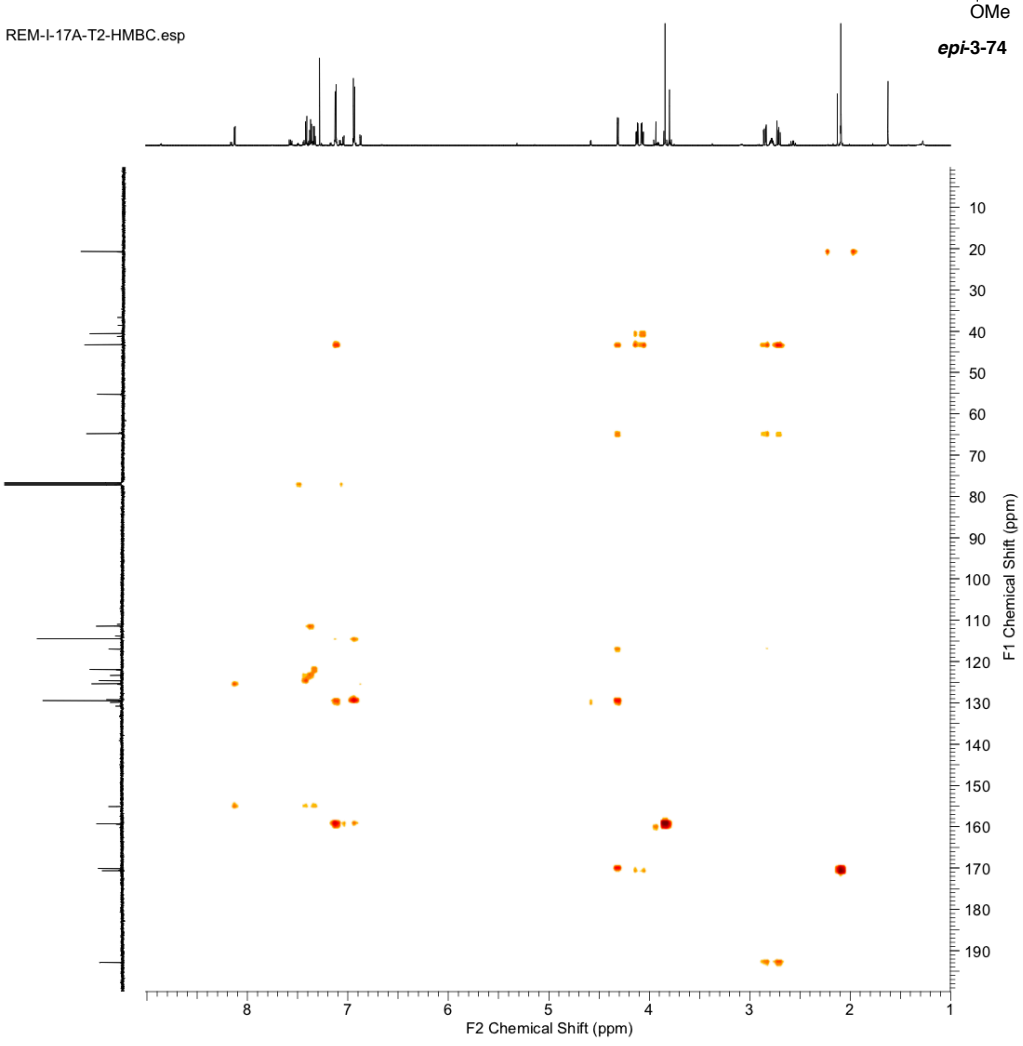
***epi*-3-74**



Acquisition Time (sec)	(0.2552, 0.0102)	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039
Date	19 Jan 2017 18:39:32		
File Name	\\Mac\Home\Documents\GA Tech Research\NMR Files\REM-I-17A-T2\5\PDATA\1\2rr		
Frequency (MHz)	(500.27, 125.81)	***Nucleus***	(1H, 13C)
Number of Transients	4	***Origin***	spect
Original Points Count	(1024, 256)	***Owner***	cwilliam
Points Count	(2048, 1024)	***Pulse Sequence***	hmbcgplpndqf
Solvent	CDCl3	***Spectrum Type***	HMBC
Sweep Width (Hz)	(4010.88, 25101.09)	***Temperature (degree C)***	24.999



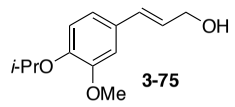
***epi*-3-74**



Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	21 Sep 2016 12:06:24
Date Stamp	21 Sep 2016 12:06:24			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\AH-I-10A\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	46.70	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.6086	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.999

AH-I-10A-1H.esp

VerticalScaleFactor = 1



3-75

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	21 Sep 2016 12:12:48
Date Stamp	21 Sep 2016 12:12:48			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\AH-I-10A\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.0605	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.999

AH-I-10A-13C.esp

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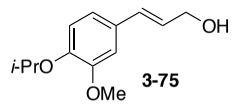
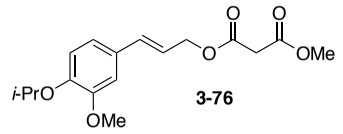


3-75

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	27 Apr 2017 12:27:44
Date Stamp	27 Apr 2017 12:27:44			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\AH-I-10B\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	29.88	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.6086	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.999

AH-I-10B-1H.esp

VerticalScaleFactor = 1



3-76

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	27 Apr 2017 12:34:08
Date Stamp	27 Apr 2017 12:34:08			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\AH-I-10B\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	36	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12570.2441	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.001

AH-I-10B-13C.esp

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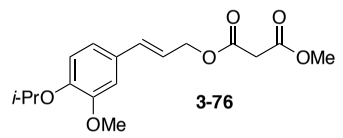
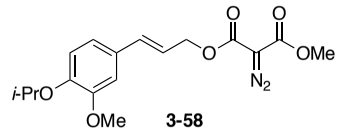


3-76

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	28 Sep 2016 15:58:56
Date Stamp	28 Sep 2016 15:58:56			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-55A\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	29.88	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3077.3035	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.000

CWW-III-55A-1H.esp

VerticalScaleFactor = 1



3-58

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	28 Sep 2016 16:03:12
Date Stamp	28 Sep 2016 16:03:12			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-55A\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	56	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12573.8770	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.001

CWW-III-55A-13C.esp

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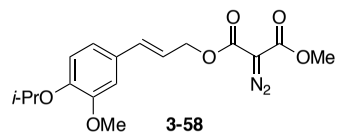

3-58

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	07 Dec 2016 12:21:04
Date Stamp	07 Dec 2016 12:21:04			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-III-75B\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	54.49	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.6931	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.002

CWW-III-75B-1H.esp

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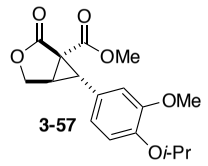

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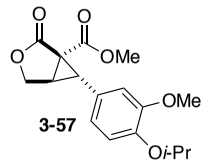

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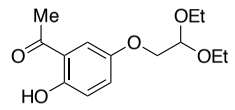

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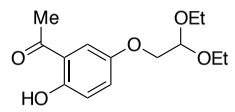

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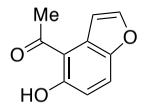

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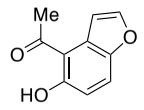

3-81

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CWW-III-68A-1H.esp

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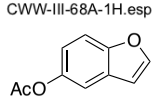

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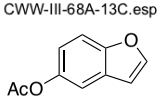

3-86

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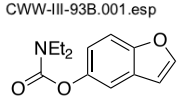

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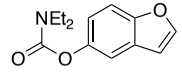

3-87

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CHAPTER 4. AN AZA-NAZAROV-LIKE PROTOCOL TOWARD THE SYNTHESIS OF THE ANTIMALARIAL FLINDEROLE ALKALOIDS

4.1 Malaria: A Devastating Disease with Need for Innovative Therapeutics

As drug-resistant bacteria and viruses continue to crop up, and infectious diseases that seemed long gone reemerge, the need for new therapeutics to combat such illnesses grows more necessary. One such infectious disease that remains a threat to humanity is malaria, a disease caused by a number of *Plasmodia* parasites (most often *P. falciparum*) that are transferred through the bites of the female *Anopholes* mosquito. It mostly found in tropical and sub-tropical regions where ~3.4 billion people reside, with an estimated 216 million cases and 445,000 dead from the disease in 2016, making it one of the most devastating infectious diseases in the world.[1] Groups most affected are young children, pregnant women, and travelers without malaria resistance. Symptoms are flu-like in nature, with high temperature fevers and shaking chills as some of the most common.[2]

Some of the most common drugs for treating malaria are shown in Figure 4.1. Two of the most commonly used antimalarials, chloroquine and artemisinin, are thought to have activity by two different mechanisms. Chloroquine acts by inhibiting the biocrystallization of hematin - a toxic metabolite produced when *Plasmodia* digest hemoglobin – into a non-toxic form encased in food vacuoles.[3] Artemisinin's activity, on the other hand, was first suspected to originate from breakdown of the endoperoxide, forming reactive oxygen species that resulted in alkylation of proteins that lead to the death of the malaria parasites.[4-5] It was later suggested, however, that its activity lies

either in (1) inhibition of the metabolism of hemoglobin, (2) the interaction of the endoperoxide with heme, preventing its polymerization/biocrystallization, or (3) interaction with hemozoin, causing its breakdown and eventual toxicity.[6] However, malaria parasites are quickly developing resistance to many current antimalarials, including some of the most potent artemisinin combination therapies. There thus remains a need to develop other therapeutics to counteract this increasing resistance throughout the globe.

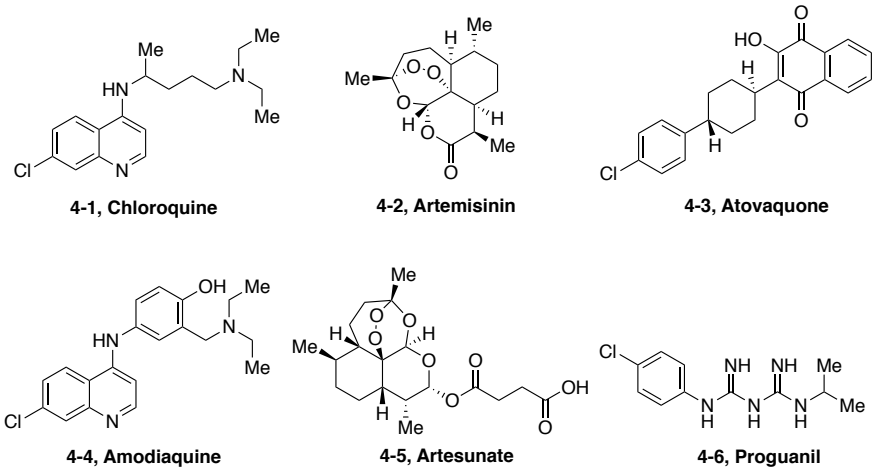
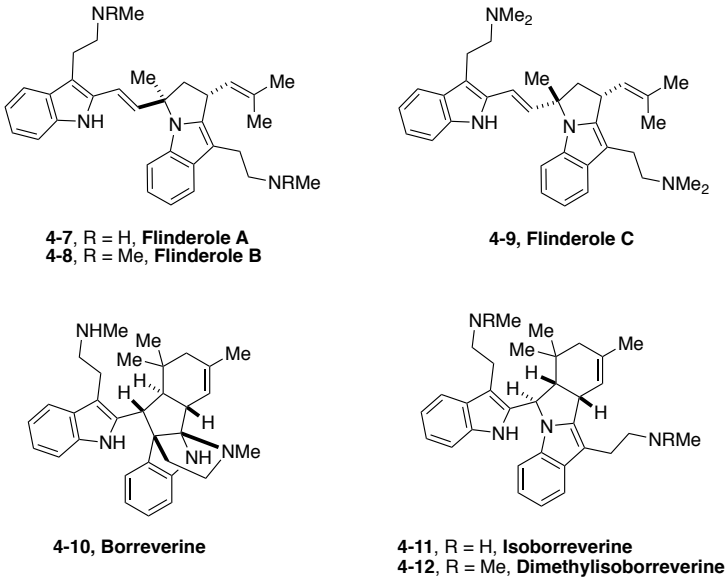


Figure 4.1 Commonly Used Antimalarial Drugs

4.1.1 Flindersial Alkaloids: Natural Products with Antimalarial Therapeutic Potential

The flindersial alkaloids isolated in 2009 from *Flindersia acuminata* and *Flindersia amboinensis* represent a valuable class of novel natural products with potent antimalarial activity. In their isolation report, three new structures were revealed, flinderoles A-C, which contained similar bistryptamine-isoprene scaffolds to the borreverine class of compounds previously isolated from *Flindersia fournieri* in 1979 (Figure 4.2).[7-8] Flinderoles A-C were effective against *P. falciparum* and against multiple chloroquine-resistant and pyramethamine-resistant strains of the parasite.[8-10] Unlike many

commonly used antimalarials, the flinderole alkaloids are not suspected to directly interfere with the hematin biocrystallization process. Instead, *in vitro* assays have suggested these alkaloids target hemoglobin metabolism much like artemisinin; in fact, the flinderole alkaloids inhibit the bioactivity of artemisinin when used in combination.[11] With these potent bioactivities and unique bistryptamine-isoprene scaffolds, these alkaloids have become attractive synthetic targets for organic chemists.



4-7, R = H, **Flinderole A**
4-8, R = Me, **Flinderole B**

4-9, Flinderole C

4-10, Borreverine

4-11, R = H, **Isoborreverine**
4-12, R = Me, **Dimethylisoborreverine**

Figure 4.2 Recently Isolated Flindersial Alkaloids

4.2 Previous Synthetic Efforts Toward Flinderoles A-C

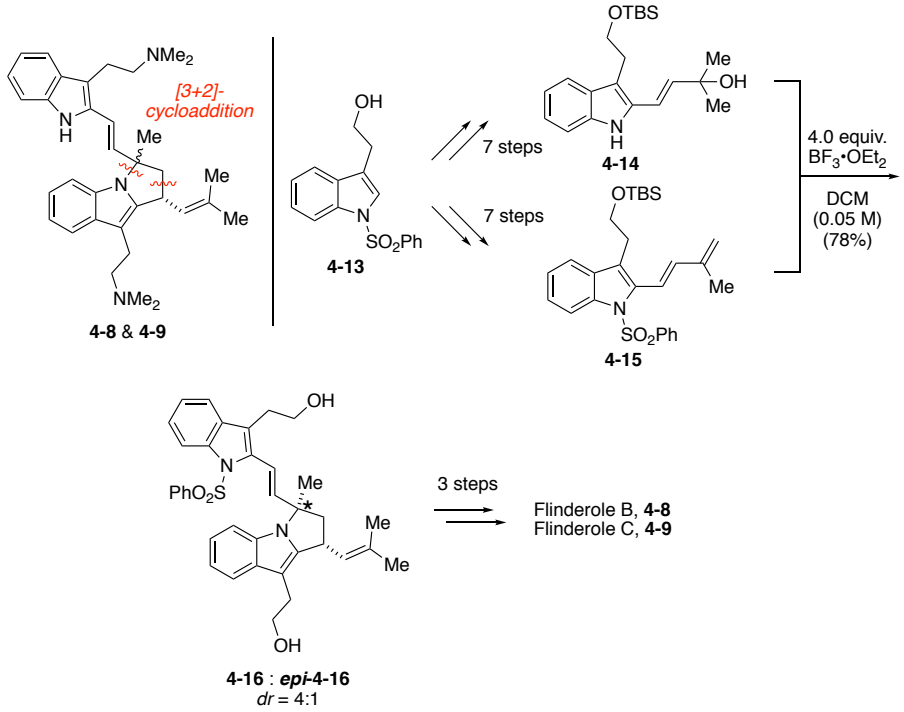
Since the isolation of the flinderoles in 2009, a number of groups have sought out their syntheses, with the groups of Dethe and May being the most prominent. Because of the sheer number of syntheses of the flinderoles at this point, only key steps of their syntheses will be discussed, along with the major strengths and weaknesses of each.

4.2.1 Dethe and Co-Workers, 2011, 2013, 2014

The first synthesis of flinderoles B and C was reported in 2011 – just two years after their isolation – by Dethe and co-workers.[12] In this synthesis, Dethe proposed a biomimetic route based upon a symmetrical retrosynthetic dissection of the molecule. Using this analysis, a Lewis acid-mediated intermolecular [3+2]-cycloaddition was designed to assemble the pyrrolo[1,2-*a*]indole scaffold (Scheme 4.1). After designing a model system to optimize conditions for the cycloaddition, six total aryl and heteroaryl substrates were also investigated, with yield ranging from 74 to 86% using 20 mol % $Cu(OTf)_2$ with the substrate at 0.05 M in DCM and diastereoselectivities up to ≥19:1. After this brief methodological study, Dethe and co-workers embarked on the synthesis of the natural products from known phenyl sulfonyl tryptophol[13] **4-13**. The two [3+2]-cycloaddition precursors were obtained in seven synthetic steps. However, BF_3•OEt_2 was employed in the key [3+2]-cycloaddition step to induce low diastereoselectivity (due to lack of coordination between the sulfonyl oxygens and indole nitrogen) to target both compounds **4-16** and ***epi*-4-16**. After only 3 more steps, flinderoles B and C were acquired in 11 total steps and 17.2% overall yield.

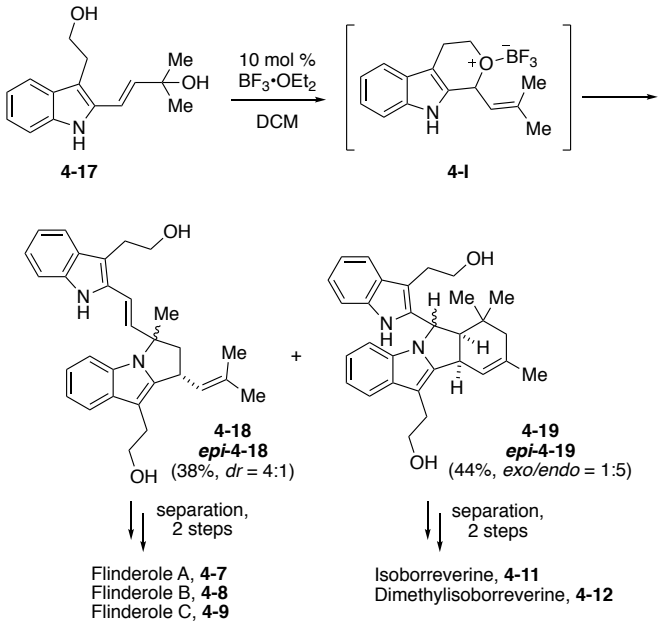
This pioneering synthesis utilizing a [3+2]-cycloaddition to assemble the major framework of the molecule would provide inspiration for a number of other biomimetic syntheses of these natural products to be discussed below. This synthesis was amenable to a number of aryl and heteroaryl substrates, which would allow for rapid assembly of other synthetic analogs of these natural products. However, this synthesis suffered from the need for protecting group installation/removal chemistry, increasing overall step

count and decreasing overall yields. As such, further work could be done to eliminate the need for protecting groups and increase yield.



Scheme 4.1 Dethe's Lewis Acid-Mediated [3+2]-Cycloaddition Toward Flinderoles B & C

Just two years after this pioneering synthesis, Dethe and co-workers utilized the same strategy they previously used toward flinderoles B and C to synthesize flinderoles A-C and the borreverine natural products isoborreverine and dimethylisoborreverine (Scheme 4.2).[14] However, this approach had one key difference – in 2013, a protecting group-free route was developed. This new route eliminated the use of protection/deprotection sequences, reducing the total step count for each of the natural products down to only six steps. However, the production of four isomers in a single step (**4-18, *epi*-4-18, 4-19, and *epi*-4-19**) reduces overall yield of a single natural product drastically and requires incredibly careful separation by column chromatography.

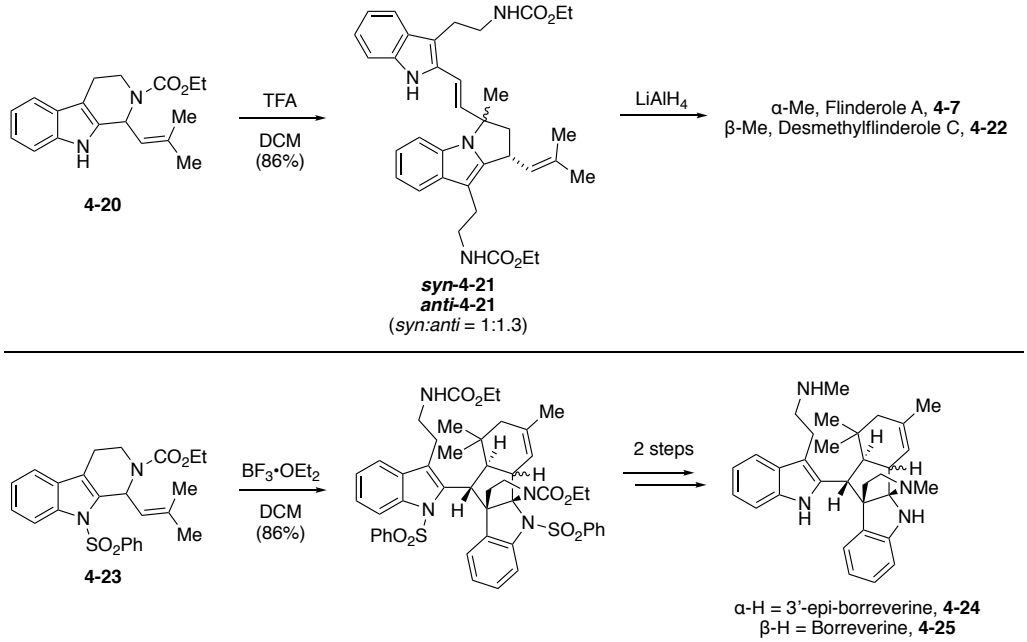


Scheme 4.2 Dethe's Protecting Group-Free Approach

In 2014, Dethe and co-workers also tackled the flinderoles one last time in their pursuit of borreverine and other bisindole alkaloids, the caulindoles, using only slightly different starting materials (Scheme 4.3).[15] In this final synthesis, Dethe developed a slightly more chemoselective approach to flinderole A; when free indole is used, cyclization occurs to form pyrrolo[1,2-*a*]indole frameworks. However, when sulfonylated indoles are used, the borreverine scaffold is formed. This final route alleviates one of the major issues in the previous synthesis – the chemoselectivity issue.

Dethe's pioneering research in the synthesis of the flinderoles has inspired many other chemists to pursue these natural products as well, whether by similar or brand new methodologies to access their pyrrolo[1,2-*a*]indole core framework. While chemoselectivity and protecting group strategies have been mostly resolved through their work, one issue still remains. When diastereoselectivity is needed, chemoselectivity is an issue. However, when chemoselectivity is needed, diastereoselectivity remains an issue.

This leaves room for others to step in and attempt to develop a chemoselective and diastereoselective route to the flinderole and borreverine natural products.

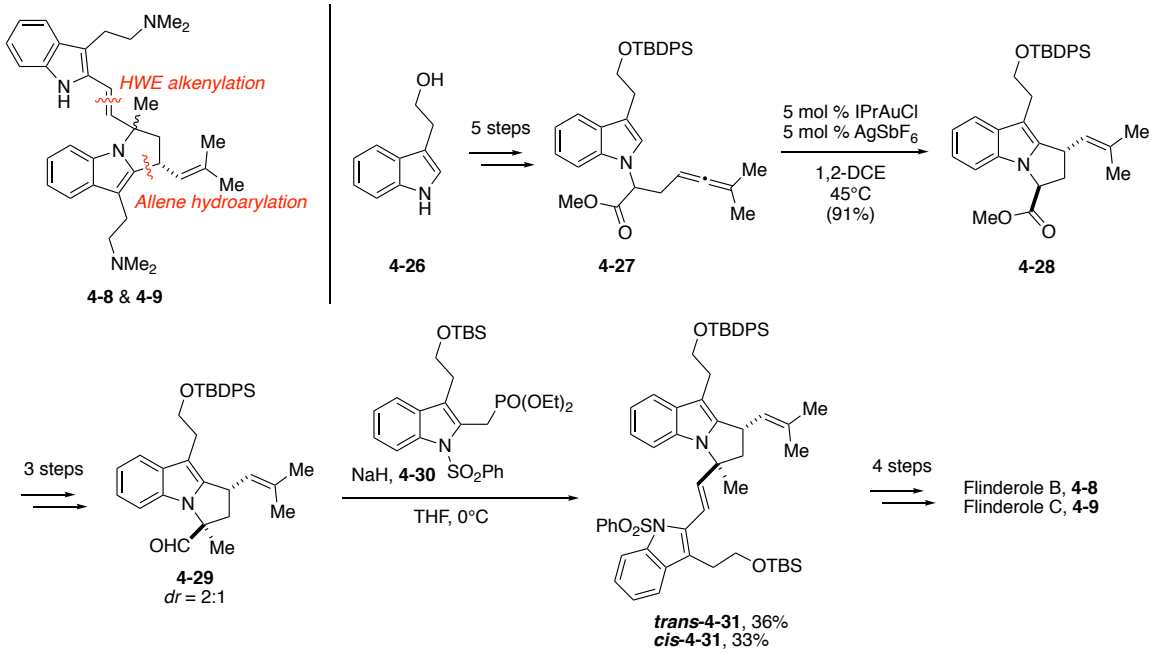


Scheme 4.3 Dethe's Final Synthesis of Flinderole A and Borreverine

4.2.2 Toste and Co-Workers, 2011

In June 2011, only four months after Dethe and co-workers' seminal report, Toste and co-workers published a second synthesis of flinderoles B and C.[16] In their synthesis, Toste devised a gold-catalyzed allene hydroarylation[17-19] to construct the pyrrolo[1,2-*a*]indole core (Scheme 4.4). Toste and co-workers embarked on their synthetic journey with the known compound tryptophol.[20] After five synthetic transformations, the key precursor **4-27** was acquired in 29% yield over the five steps. In the key allene hydroarylation step, triphenylphosphinegold(I) was initially used with no positive results. After exchanging the catalyst with the electropositive NHC catalyst IPrAuCl, the reaction proceeded smoothly. Compound **4-27** was cyclized using 5 mol% IPrAuCl and 5 mol % $AgSbF_6$, giving the key intermediate **4-28** in 91% yield as a single *trans* diastereomer.

Although 2 mol % of the catalyst system could also be used, yields dropped to 81% yield and significant amount of diene side products were observed. With the core pyrrolo[1,2-*a*]indole scaffold in hand, the rest of the synthesis proceeded rather smoothly. The final key step was a Horner-Wadsworth-Emmons alkenylation of the 2-(methylindole)phosphonate **4-30**; fortunately this transformation was known through the work of Srinivasan and co-workers, giving Toste and co-workers a set of conditions with which to complete this step in 36% and 33% yield for ***trans*-4-31** and ***cis*-4-31**, respectively. All in all, Toste and co-workers completed the synthesis of flinderoles B and C in 14 total steps in the longest linear sequence at an overall 4% yield.



Scheme 4.4 Toste's Allene Hydroarylation Toward Flinderoles B & C

Toste and co-workers in their synthesis provided a beautiful display of the application of gold-catalyzed hydroarylation of allenes in order to synthesize flinderoles B and C. This method provides yet another alternative route toward pyrrolo[1,2-*a*]indole scaffolds; however, Toste's route is longer than that previously published[12] and has a

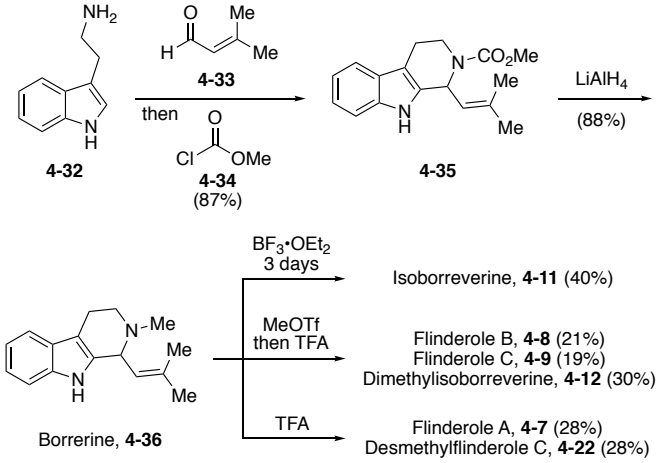
drastically low overall yield, mostly due to low yielding steps late in the synthesis. This route also includes a number of protection/deprotection sequences, increasing the step count. While this was an excellent showcase of Toste's methodology, other methodologies could be developed to access the pyrrolo[1,2-*a*]indole core scaffold, allowing for more modular syntheses of flinderoles B and C and their analogs.

4.2.3 May and Co-Workers, 2012

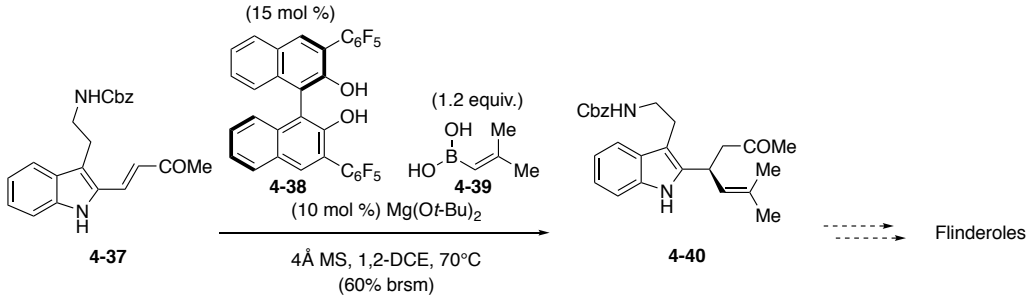
In 2012, May and co-workers reported another biomimetic total synthesis of the flindersial alkaloids.[21] Vallakati and May hypothesized that the flinderole scaffolds emerged from the dimerization of another natural product, borrerine, via a ring-opening isomerization and either a formal [3+2]-cycloaddition (to form the flinderoles) or a Diels-Alder cycloaddition (to form the borreverines). Using this route, flinderoles A-C, desmethylflinderole C, isoborreverine, and dimethylisoborreverine were obtained in only three total steps from commercially available tryptamine (Scheme 4.5). Tryptamine was reacted with 2-methyl-2-butenal and then methyl carbonochloridate to form **4-33**. Reduction with $LiAlH_4$ gave the key intermediate, borrerine, which, depending on the reaction conditions, gave each of the flindersial alkaloids (without borreverine).

Since this publication, May and co-workers have been seeking an enantioselective route toward the flindersial alkaloids.[22] While it seems they are produced racemically in biological systems, it is prudent to understanding the bioactivity in context of the correct enantiomer of the natural product. To accomplish this, they devised a strategy to set the stereochemistry of the benzylic (2-methyl)propenyl group before the synthesis of the pyrrolo[1,2-*a*]indole scaffold. Thus far, a stereoselective synthesis of the key

intermediate toward the core framework has been completed (Scheme 4.6), though no other work toward an enantioselective synthesis has been reported.



Scheme 4.5 May's Synthesis of the Flindersial Alkaloids

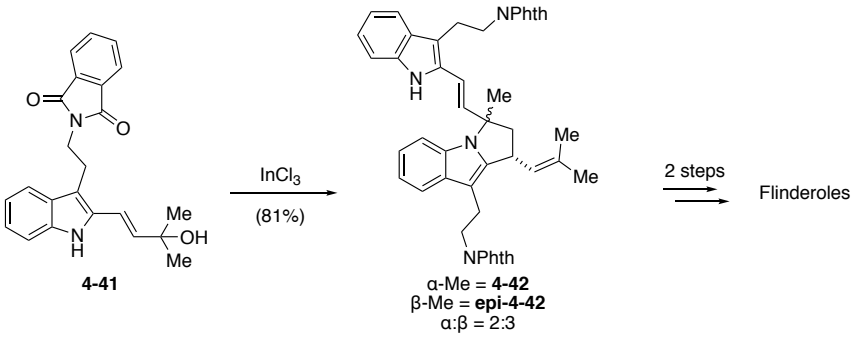


Scheme 4.6 May's Synthetic Efforts Toward an Enantioselective Synthesis of the Flinderoles

May's synthetic efforts represent some of the most powerful methods to access the flindersial alkaloids to date. However, May's strategy suffers from significant chemoselectivity issues. A number of products are isolated from a single reaction, leading to the need for careful separations. However, his strategy is very efficient, with little to no byproducts or degradation observed under optimized conditions. May and co-workers are the first and only group so far to attempt an enantioselective synthesis of the flindersial alkaloids. There still remains a need for a more chemoselective method, and further optimization and synthetic work toward an enantioselective route needs to be completed.

4.2.4 Pandey and Co-Workers, 2016

In 2016, Pandey and co-workers published the most recent synthesis of the flinderole alkaloids (Scheme 4.7).[23] In this report, Pandey utilized a similar intermediate to that use by Dethe and co-workers in 2011, only replacing a protected tryptophol with a phthalimide-protected tryptamine **4-41**. $InCl_3$ was used to induce a formal [3+2]-cycloaddition as the key step, with each of the flinderoles being obtained in only six steps. This represents yet another biomimetic route to the flinderoles; however, this route is plagued by the use of the phthalimide protecting group, adding to step count with protection and removal. Pandey's route is also not diastereoselective, leading to both flinderole precursors that must be carefully separated. There again remains a need for a diastereoselective route to effectively acquire only a single one of the flinderoles.



Scheme 4.7 Pandey's Synthesis of the Flinderoles

4.3 Methods Toward the Flinderole Framework: Pyrrolo[1,2-*a*]indoles

The key framework of the flinderoles is the central pyrrolo[1,2-*a*]indole core, a privileged scaffold in the realm of indole alkaloids. A current Reaxys search revealed approximately 36 known alkaloids containing this framework, each having it own unique structure and set of bioactivities. Many methods have been devised to access this core scaffold, some of which have already been discussed in detail in section 4.2 in the

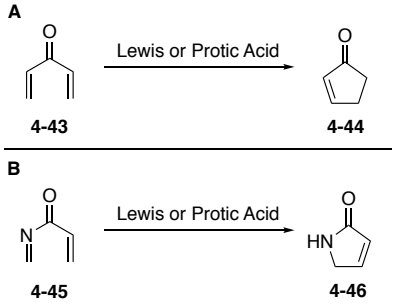
synthesis of the flinderoles. To my knowledge, only one review has been published detailing methodologies (prior to 2016) to access the pyrrolo[1,2-*a*]indoles,[24] and many other communication/articles have been published since.[25-35] With a plethora of methods reported to access this scaffold and the potent bioactivity of many of these natural products, it is no surprise that the flinderoles have remained a popular target for synthetic chemists.

4.3.1 An Aza-Nazarov-Like Protocol Toward the Pyrrolo[1,2-a]indole Core

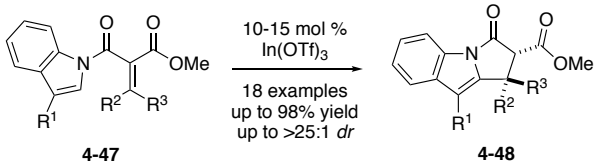
The Nazarov reaction represents a power method to synthesize densely functionalized cyclopentenones (Scheme 4.8A; for greater detail, see Chapter 1.2.2). Aza variants of the Nazarov reaction also represent a facile method to obtain densely functionalized lactams (Scheme 4.8B). In 2011, France and co-workers reported an aza-Nazarov-like protocol toward the synthesis of densely functionalized pyrrolo[1,2-*a*]indoles from β-amidoesters.[36] Using $In(OTf)_3$, these β-amidoesters were activated to induce an intramolecular Friedel-Crafts alkylation of the indole amide in a Michael-like fashion, forming the desired pyrrolo[1,2-*a*]indole framework (Scheme 4.9). Considering the catalytic nature of this protocol, breadth of scope, and high diastereoselectivity, we believed that this aza-Nazarov-like protocol represented a novel, highly modular, diastereoselective method toward the flinderole natural products.

The aza-Nazarov-like, Friedel-Crafts-type (henceforth referred to as ANFC) cyclization reaction of α-sulfonylamides is completely unexplored. In fact, the Nazarov reaction of α-sulfonylketones is also very underexplored; to our knowledge, the only known report of Nazarov cyclizations on α-sulfonylketones was published by Frontier in 2008, with only a single α-sulfonylketone substrate (Scheme 4.10).[37] As such, the

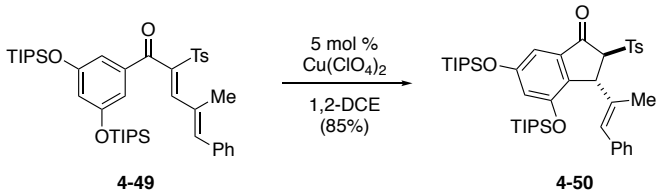
synthesis of the flinderole natural products utilizing this architecture will have a four-fold impact: (1) the addition of a second electron-withdrawing group in the Nazarov cyclization should lower activation energy, increasing the likelihood of achieving catalysis, (2) this will further expand the chemical space of Nazarov-like reactions to α-sulfonylcarbonyl substrates, (3) sulfones are useful synthetic handles, providing a pathway toward Julia olefinations, reductive desulfonylations, and the acidic nature of sulfone α-protons allow for effective α-functionalizations, and (4) with the use of sulfonyl protecting groups throughout the rest of the flinderole synthesis, all sulfonyl groups can be removed in a single, global deprotection step.



Scheme 4.8 Nazarov vs. an Aza-Nazarov Cyclization Variant



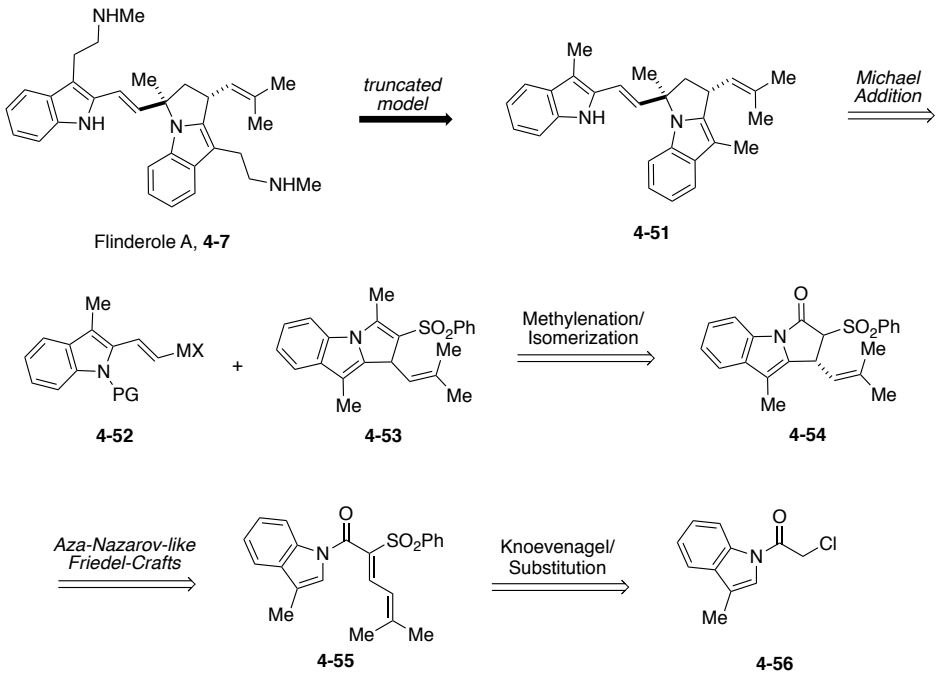
Scheme 4.9 France's Previous Aza-Nazarov-Like, Friedel-Crafts Cyclization Methodology



Scheme 4.10 Frontier's Previous Methodology

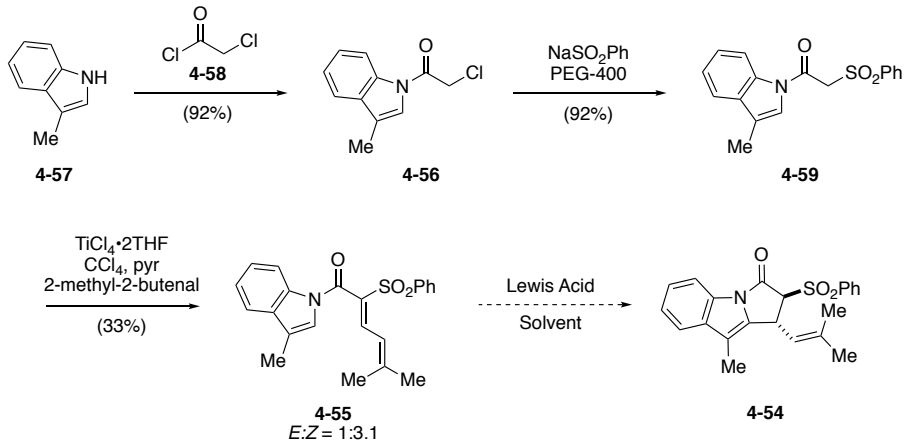
4.4 Current Progress Toward the Flinderole Alkaloids Utilizing an Aza-Nazarov-Like Approach

While many short synthetic routes to the flinderoles have been established, we hoped to develop a synthesis focusing on alleviating one of the major issues of previous syntheses – diastereoselectivity. We also hoped to improve on the modularity of previous syntheses, allowing for the synthesis of many unnatural analogs with the intention of improving bioactivity utilizing this novel α-sulfonylamide architecture. We first devised a synthetic route through using the retrosynthetic analysis shown in Scheme 4.11. Flinderole A was chosen due to the *trans* relationship of the two olefins across the pyrrole ring. In order to initially simplify the synthesis, a model system was designed using 3-methylindole as a major template. We envisioned **4-51** being synthesized via a Michael addition of the organometallic **4-52** on the unsaturated sulfone **4-53**. The desired *trans* stereochemistry is expected to be favored due to steric effects; however, both *cis* and *trans* diastereomers should be obtained. The key intermediate **4-53** would be derived from a carbonyl methylenation using a Wittig-type reaction and alkene isomerization of the ketone **4-54**. Compound **4-54** is derived from the ANFC cyclization of the α-sulfonylamide **4-55** obtained from a Knoevenagel condensation. The sulfonyl group would be installed via a simple substitution reaction on the α-chloroamide **4-56**.



Scheme 4.11 Retrosynthetic Analysis of Flinderole A

To begin the synthesis of the model substrate **4-51**, acylation of 3-methylindole with α-chloroacetic acid chloride afforded the desired intermediate **4-56** in 92% yield. Using a protocol developed by Venkateswarlu,[38] sodium benzenesulfinate displaced chloride in the presence of PEG-400 to afford the α-sulfonylamide **4-57**. Upon obtaining **4-57**, all attempts at a protic acid-promoted Knoevenagel condensation conditions to obtain **4-53** resulted only in the recover of starting material. Thus, a $TiCl_4$-promoted Knoevenagel condensation was used; however, this reaction was incredibly inefficient and resulted in a 1:3.1 *E:Z* diastereomeric mixture. The material was enough the carry forward for the investigation of the Lewis acid-catalyzed ANFC cyclization.

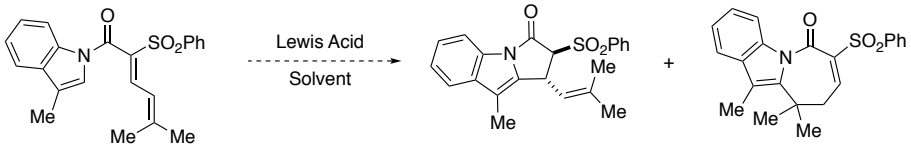


Scheme 4.12 Synthesis of Aza-Nazarov Substrate **4-55**

Next, several Lewis acids were screened for their viability as an ANFC cyclization catalyst. At this stage, only 3+ salts were screened, partly due to their success in France's previous protocol. In entries 1-3 of Table 4.1, no reaction was observed with any of the 3+ salts at room temperature in DCM. At this stage, it was evident that this reaction was not a favorable reaction at room temperature; a solvent switch to 1,2-DCE was made and each subsequent reaction was conducted at reflux. Gratifyingly, the formation of the desired product was observed at these higher temperatures. However, reaction times were much longer than desirable, with the shortest time until full conversion (by TLC analysis) was 3 days. The highly oxophilic 3+ salts $Al(OTf)_3$ and $Ga(OTf)_3$ provide the best yields of 57% and 54% respectively after 3 days. Interestingly, the indole-fused azepinone byproduct **4-60** was also observed under these reaction conditions that, to our knowledge, is the first reactivity of this type to be observed on these diene systems. The highest yielding catalyst, $Al(OTf)_3$, was also retested at 0.3 M in 1,2-DCE to increase the effective concentration of the catalyst. As a result, the yield increased from 57% to 67%. This reaction represents the first ANFC cyclization on α-sulfonylamide substrates and also a novel method to access indole-fused azepinones as

observed by the byproduct **4-60**. Unfortunately, the reproducibility of this reaction is not consistent. More optimizations for this step remain to be completed, with more Lewis acids to be screened, and full solvent, temperature, and concentration screens.

Table 4.1 ANFC Cyclization Lewis Acid Screen



4-55
E:*Z* = 1:3.1

4-54

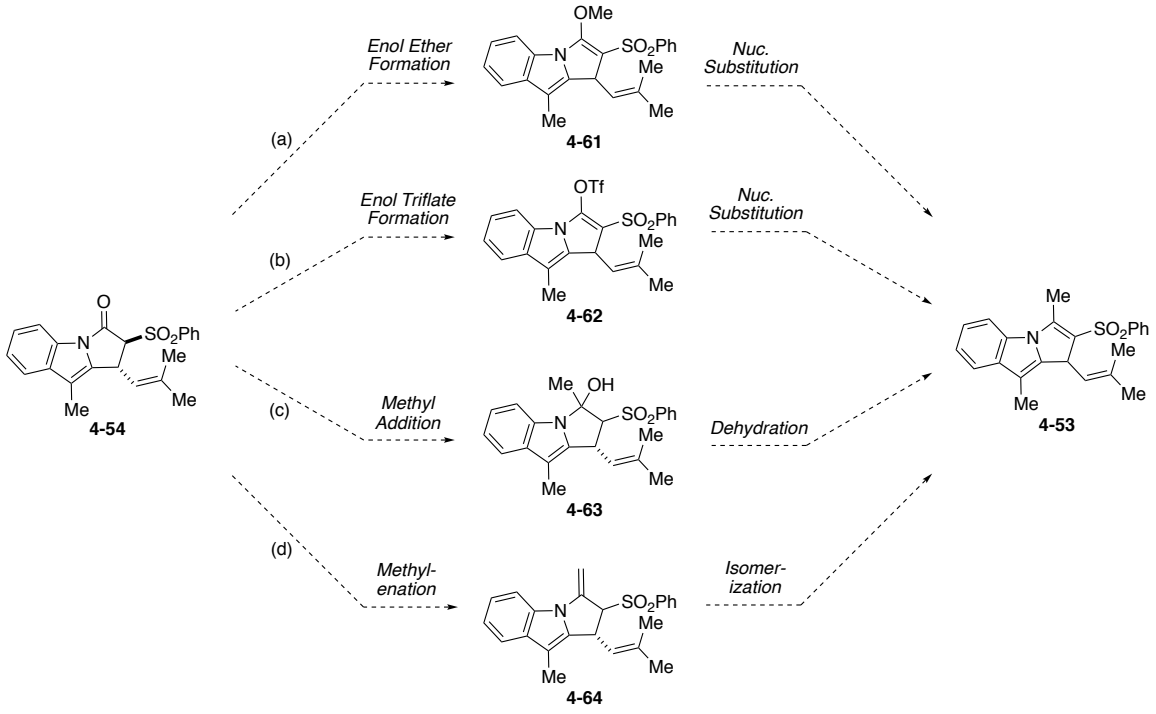
4-60

Entry	Lewis Acid	Temp (°C)	Solvent	Yield (%) 4-54	Yield (%) 4-60	Time (days)
1	$In(OTf)_3$	23	DCM	0	0	--[a]
2	$Sc(OTf)_3$	23	DCM	0	0	--[a]
3	$Al(OTf)_3$	23	DCM	0	0	--[a]
4	$In(OTf)_3$	84	1,2-DCE	48	0	3
5	$Sc(OTf)_3$	84	1,2-DCE	30	0	3
6	$Al(OTf)_3$	84	1,2-DCE	57 (67)[b]	14 (12)[b]	3
7	$Ga(OTf)_3$	84	1,2-DCE	54	16	3
8	$Yb(OTf)_3$	84	1,2-DCE	21	0	2
9	$La(OTf)_3$	84	1,2-DCE	0	0	--[a]

[a] No conversion observed after >24 hours. [b] Reaction performed at 0.3 M.

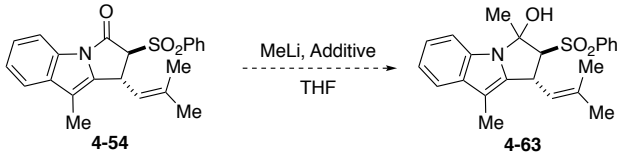
Upon obtaining a reasonable amount of **4-54**, a number of different pathways toward methylation were explored (Scheme 4.13). In pathway a, the formation of an alkyl enol ether was explored, with the expectation of using an organometallic reagent for conjugate addition to the vinyl sulfone[39-41] **4-61**. However, all attempts at formation of the alkyl enol ether resulted in methylation of the α-carbon using methyl triflate or dimethyl sulfate. In pathway b, the formation of an enol triflate was expected to provide a handle for cross coupling, leading to the desired vinyl sulfone **4-53**. However, after an attempt to form the enol triflate using triflyl chloride, crude ^{1}H NMR gave inconclusive insight into enol triflate formation. In pathway c, an organometallic methyl reagent would

be used to generate the tertiary alcohol **4-63** which would be carried forward for condensation to for **4-53**. The results of all attempts to synthesize the tertiary alcohol are summarized in Table 4.2, with no positive results. Finally, in pathway d, olefination of the ketone was expected to give the β,γ-unsaturated ketone. Wittig olefinations have been generally problematic with amides for the formation of enamines; olefinations with Tebbe's reagent or the Petasis reagent, on the other hand, have been a powerful method for forming enamines from amides. It was also expected that an olefin isomerization would need to be investigated. However, upon reacting **4-54** with Tebbe's reagent, it was discovered that no only had the olefination occurred, but isomerization of the alkene had also taken place in the same pot in 23% yield (Scheme 4.14). Further optimization also needs to be conducted for this step with other reagents such as the Petasis reagent. As such, the key pyrrolo[1,2-*a*]indole intermediate **4-53** had been synthesized.



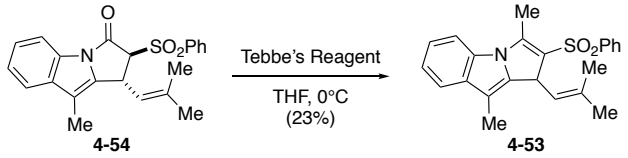
Scheme 4.13 Synthetic Pathways to **4-53**

Table 4.2 Summary of Attempted Methyl Additions to Carbonyl



Entry	MeLi (equiv.)	Additive (equiv.)	Temp. (°C)	Yield (%)
1	1.2	$CeCl_3 \cdot 7H_2O$ (1.3)	-78	--[a]
2	1.2	$CeCl_3$ (2.0)	-78	--[a]
3	3.1	--	-78 to rt	--[b]

[a] No conversion observed by TLC or NMR. [b] An intractable mixture was obtained.



Scheme 4.14 Olefination/Olefin Isomerization with Tebbe's Reagent

4.5 Summary of Progress Toward the Flinderoles Utilizing an ANFC Approach

In conclusion, a highly modular, diastereoselective approach toward the flinderole natural products has been proposed. Using 3-methylindole, the synthesis of a key intermediate of the model substrate, the pyrrolo[1,2-*a*]indole containing an unsaturated cyclic sulfone, has been completed. An ANFC cyclization protocol was used to generate the pyrrolo[1,2-*a*]indole core scaffold using $Al(OTf)_3$ as the Lewis acid catalyst. Using Tebbe's reagent, an olefination/isomerization cascade protocol was serendipitously discovered, leading to the key intermediate needed for the final organometallic conjugate addition step to synthesize the bisindole framework of the flinderoles.

Moving forward, a number of optimizations still need to be completed, along with completion of the model substrate. Because of the number of low yielding, irreproducible steps thus far, scalability remains an issue that also needs to be addressed. Once these issues are alleviated, the synthesis of the flinderole natural products using a tryptamine

substrate can begin and should rapidly translate from the steps shown in the progress toward the synthesis of this model system.

4.6 Experimental Section

4.6.1 Synthetic Methods

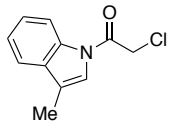
Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-65μm) or preparative thin-layer chromatography (prep-TLC) using Silicycle silica gel F_{254} (1000 μm) plates and solvents indicated as eluent with 1-5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light.

Infrared (IR) spectra were obtained using a Shimadzu IRAffinity-1S FTIR with a Specac Quest ATR attachment. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, or Bruker 400 MHz, 500 MHz, and 800 MHz spectrometers with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer using $PhCF_3$ as an external standard. ^{1}H and ^{19}F NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Mass spectra were obtained MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of 10,000 using PFK

(perfluorokerosene) as an internal calibrant. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).

General Procedure for Lewis Acid Screen:

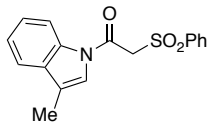
To a dry, nitrogen-purged round bottom flask was added the appropriate Lewis acid (20 mol %). The unsaturated α-sulfonylamide (1.0 equiv.) was dissolved in the appropriate solvent (0.1 M). The reaction was heated to the appropriate temperature until the starting material was consumed (monitored by TLC). Water was then added to the reaction mixture and diluted with DCM. The mixture was extracted three times with DCM, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was then purified via flash chromatography and concentrated.



4-56

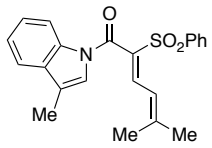
2-chloro-1-(3-methyl-1*H*-indol-1-yl)ethan-1-one: Indole (15.0 g, 0.114 mol) was dissolved in toluene (114 mL) and chloroacetyl chloride (22.7 mL, 0.286 mol) was added. The mixture was heated to reflux overnight and concentrated. The mixture was purified by flash chromatography (R_f = 0.58, 25% EtOAc/Hexane) to give the title compound (21.8, 92% yield) as a brown solid. **^{1}H NMR** (300MHz, $CDCl_3$) δ = 8.41 (d, *J* = 7.9 Hz, 1 H), 7.54 - 7.47 (m, 1 H), 7.43 - 7.29 (m, 2 H), 7.16 (s, 1 H), 4.52 (s, 2 H), 2.29 (d, *J* = 1.3 Hz, 3 H). **^{13}C NMR** (75MHz, $CDCl_3$) δ = 163.6, 135.9, 131.3, 125.6, 124.1, 120.9, 119.9, 119.0, 116.6, 42.4, 9.7. **IR:** 3339 (w), 3100 (w), 2994, (w), 2951 (w),

2922 (w), 1708 (s), 1391 (s), 1207 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{11}H_{10}ClNO$, 207.0451; found 207.0450.



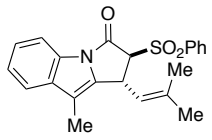
4-59

1-(3-methyl-1*H*-indol-1-yl)-2-(phenylsulfonyl)ethan-1-one: Prepared according to a previously reported method.[38] Chloroacetyl indole (393 mg, 1.89 mmol) and sodium benzenesulfinate (476 mg, 2.90 mmol) was suspended in PEG-400 (7.5 mL). The mixture was heated to 50°C and stirred overnight. The reaction was quenched with water, extracted three times with EtOAc, washed with water, dried over Na_2SO_4, filtered through celite, and concentrated. The crude solid was purified by flash chromatography (R_f = 0.25, 25% EtOAc/Hexane) to give the title compound (462 mg, 78% yield) as a white solid. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.31 (d, *J* = 5.2 Hz, 1 H), 7.96 - 7.91 (m, 2 H), 7.69 (tt, *J* = 1.2, 7.5 Hz, 1 H), 7.58 - 7.53 (m, 2 H), 7.52 - 7.47 (m, 1 H), 7.36 - 7.31 (m, 2 H), 7.23 (s, 1 H), 4.63 (s, 2 H), 2.27 (d, *J* = 1.2 Hz, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 158.9, 138.2, 135.9, 134.5, 131.8, 129.3, 128.6, 125.6, 124.5, 122.0, 120.2, 119.0, 116.8, 62.3, 9.7. **IR:** 3132 (w), 2995 (w), 2941 (w), 1686 (s), 1307 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{17}H_{15}NO_3S$, 313.0773; found 313.0777.



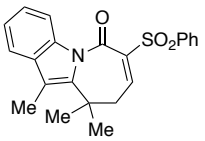
4-55
E:*Z* = 1:3.1

(*Z*)-5-methyl-1-(3-methyl-1*H*-indol-1-yl)-2-(phenylsulfonyl)hexa-2,4-dien-1-one: β-Amidosulfone **4-59** (500 mg, 1.60 mmol) was dissolved in THF (35 mL) and cooled to 0°C. $TiCl_4$•2THF (1.07 g, 3.20 mmol) and carbon tetrachloride (0.31 mL, 3.20 mmol) were added and stirred for 1 hour at 0°C. 3-methyl-2-butenal (0.15 mL, 1.60 mmol) was added slowly and stirred for 1 hour at 0°C. Pyridine (0.51 mL, 6.38 mmol) was then added at 0°C, warmed to room temperature, and stirred 3 days. The reaction was quenched with water, extracted three times with Et_2O, washed with sat. aq. $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (R_f = 0.42, 25% EtOAc/Hexane) to give the title compound (198 mg, 33% yield) as a yellow solid. *(Diastereomeric ratio = 3.1:1)* **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.44 - 8.34 (m, 1.29 H), 8.12 - 8.07 (m, 0.65 H), 7.94 - 7.89 (m, 1.94 H), 7.81 (d, *J* = 12.2 Hz, 0.99 H), 7.66 - 7.60 (m, 1.34 H), 7.59 - 7.49 (m, 3.97 H), 7.39 - 7.31 (m, 2.68 H), 7.24 (d, *J* = 1.5 Hz, 0.31 H), 7.18 - 7.14 (m, 0.35 H), 7.13 - 7.10 (m, 0.32 H), 7.03 (s, 0.93 H), 5.75 (quind, *J* = 1.3, 12.3 Hz, 0.99 H), 2.27 (d, *J* = 1.5 Hz, 0.97 H), 2.23 (d, *J* = 1.5 Hz, 3.00 H), 2.06 - 2.01 (m, 3.97 H), 1.85 - 1.80 (m, 3.96 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 162.7, 161.0, 155.6, 154.9, 141.5, 140.2, 139.9, 138.2, 136.0, 135.5, 133.6, 133.6, 133.3, 132.4, 132.3, 132.0, 129.1, 129.1, 128.2, 128.0, 125.2, 124.4, 124.2, 123.7, 123.5, 119.5, 119.1, 119.0, 119.0, 118.9, 118.8, 116.8, 116.6, 27.7, 27.1, 19.5, 19.0, 9.7. **IR:** 3067 (w), 2972 (w), 2918 (w), 2855 (w), 1674 (m), 1624 (m), 1578 (m), 1447 (s), 1144 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{22}H_{21}NO_3S$, 379.1242; found 379.1250.



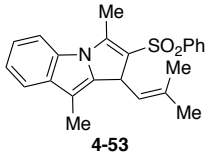
4-54

(1*S*,2*R*)-9-methyl-1-(2-methylprop-1-en-1-yl)-2-(phenylsulfonyl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indol-3-one: $Al(OTf)_3$ (125 mg, 0.26 mmol) was added to a flask and unsaturated sulfone **4-55** (498 mg, 1.31 mmol) was dissolved in 1,2-DCE (4.4 mL) and added to the catalyst. The mixture was heated to reflux for 3 days and concentrated. The crude residue was purified by flash chromatography *(R_f* = 0.39, 20% EtOAc/Hexane) to give the title compound (335 mg, 67% yield) as a yellow solid. *(Diastereomeric ratio = 5.4:1)* **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.17 - 8.14 (m, 0.11 H), 8.03 - 7.98 (m, 1.97 H), 7.96 - 7.91 (m, 1.50 H), 7.72 - 7.63 (m, 1.32 H), 7.62 - 7.52 (m, 2.67 H), 7.43 - 7.40 (m, 1.13 H), 7.33 - 7.27 (m, 2.35 H), 5.12 (tdd, *J* = 1.4, 2.8, 10.0 Hz, 1.00 H), 4.98 - 4.92 (m, 1.16 H), 4.38 (d, *J* = 2.4 Hz, 0.16 H), 4.83 (d, *J* = 0.6 Hz, 0.18 H), 4.27 (d, *J* = 3.7 Hz, 1.02 H), 2.24 - 2.21 (m, 0.56 H), 2.10 (d, *J* = 1.2 Hz, 3.00 H), 1.93 (d, *J* = 1.2 Hz, 3.02 H), 1.83 - 1.77 (m, 3.71 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 161.2, 137.4, 136.9, 136.5, 134.5, 130.3, 129.4, 129.2, 129.1, 129.1, 124.7, 124.0, 120.8, 118.9, 114.0, 111.0, 76.2, 34.0, 25.7, 18.3, 7.8. **IR:** 3061 (w), 2972 (w), 2918 (w), 2864 (w), 1732 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{22}H_{21}NO_3S$, 379.1242; found 379.1250.



4-60

10,10,11-trimethyl-7-(phenylsulfonyl)-9,10-dihydro-6*H*-azepino[1,2-*a*]indol-6-one: $Al(OTf)_3$ (125 mg, 0.26 mmol) was added to a flask and unsaturated sulfone **4-55** (498 mg, 1.31 mmol) was dissolved in 1,2-DCE (4.4 mL) and added to the catalyst. The mixture was heated to reflux for 3 days and concentrated. The crude residue was purified by flash chromatography *(R_f* = 0.19, 20% EtOAc/Hexane) to give the title compound (58 mg, 11% yield) as a yellow solid. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.20 - 8.16 (m, 1 H), 8.04 - 8.00 (m, 2 H), 7.90 (t, *J* = 6.9 Hz, 1 H), 7.61 - 7.57 (m, 1 H), 7.54 - 7.50 (m, 2 H), 7.41 - 7.38 (m, 1 H), 7.27 - 7.23 (m, 2 H), 2.76 (d, *J* = 7.0 Hz, 2 H), 2.37 (s, 3 H), 1.54 (s, 6 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 161.2, 147.6, 141.2, 140.6, 138.7, 136.9, 133.3, 131.7, 128.7, 128.6, 125.3, 124.0, 117.8, 117.1, 116.8, 41.6, 39.4, 29.0, 11.4. **IR:** 3067 (w), 2957 (w), 2866 (w), 1678 (s), 1306 (s), 1285 (s) cm^{-1}. **HRMS (EI)** $[M]^+$ m/z: Calcd. for $C_{22}H_{21}NO_3S$, 379.1242; found 379.1256.



4-53

(*S*)-3,9-dimethyl-1-(2-methylprop-1-en-1-yl)-2-(phenylsulfonyl)-1*H*-pyrrolo[1,2-*a*]indole: β-Amidosulfone **4-54** (99 mg, 0.26 mmol) was dissolved in THF (1.0 mL) and cooled to 0°C. Tebbe's reagent (0.63 mL, 0.5 M in toluene, 0.32 mmol) was added and stirred at 0°C for 4 hours. The mixture was diluted with EtOAc, quenched with 0.1 M NaOH, extracted three times with EtOAc, washed with brine, filtered through celite, and concentrated. The crude residue was purified by flash chromatography (R_f = 0.81, 30% EtOAc/Hexane) to give the title compound (23 mg, 23% yield) as a yellow solid. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.86 - 7.82 (m, 2 H), 7.60 - 7.56 (m, 1 H), 7.54 - 7.51 (m, 1

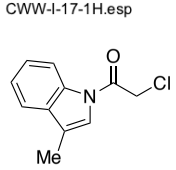
H), 7.50 - 7.46 (m, 3 H), 7.23 - 7.15 (m, 2 H), 4.83 - 4.77 (m, 1 H), 4.38 - 4.33 (m, 1 H), 3.01 (d, J = 1.8 Hz, 3 H), 2.11 (d, J = 2.1 Hz, 3 H), 1.88 (d, J = 1.2 Hz, 3 H), 1.58 (d, J = 1.5 Hz, 3 H). **^{13}C NMR** (126MHz, $CDCl_3$) δ = 148.5, 143.4, 139.6, 135.8, 134.2, 132.5, 130.8, 128.6, 127.1, 122.3, 121.2, 120.7, 119.4, 119.2, 110.9, 107.7, 41.3, 25.6, 18.2, 12.9, 7.9. **IR:** 3063 (w), 2970 (w), 2928 (w), 2870 (w), 1717 (w), 1695 (w), 1614 (w), 1138 (s) cm^{-1}. **HRMS (ESI)** $[M+H]^+$ m/z: Calcd. for $C_{23}H_{24}NO_2S$, 378.1522; found 378.1520.

4.6.2 NMR Spectra

Acquisition Time (sec)	3.5504	***Comment***	Std Proton parameters			***Date***	Jun 4 2013
Date Stamp	Jun 4 2013	***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW_I_17.fid\fid				
Frequency (MHz)	300.22	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	17053
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1802.2225	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4803.07	***Temperature (degree C)***	AMBIENT TEMPERATURE

CWW-I-17-1H.esp

VerticalScaleFactor = 1

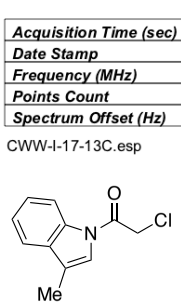


4-56

Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jun 4 2013
Date Stamp	Jun 4 2013	***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW_I_17_13C.fid\fid				
Frequency (MHz)	75.50	***Nucleus***	13C	***Number of Transients***	244	***Original Points Count***	23560
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	38.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	7923.3740	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	18115.94	***Temperature (degree C)***	AMBIENT TEMPERATURE

CWW-I-17-13C.esp

VerticalScaleFactor = 1

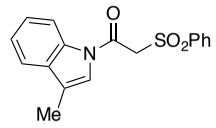


4-56

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	23 May 2017 13:23:12
Date Stamp	23 May 2017 13:23:12			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-24\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	54.49	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.6931	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.997

CWW-I-24-1H.esp

VerticalScaleFactor = 1

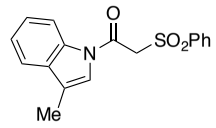


4-59

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	23 May 2017 13:27:28
Date Stamp	23 May 2017 13:27:28			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-24\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	64	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12571.1523	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.000

CWW-I-24-13C.esp

VerticalScaleFactor = 1

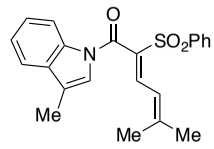


4-59

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	10 May 2017 17:02:56
Date Stamp	10 May 2017 17:02:56			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-74\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	54.49	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.6931	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.005

CWW-I-74-1H.esp

VerticalScaleFactor = 1

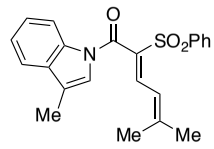


4-55
E:*Z* = 1:3.1

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	10 May 2017 17:07:12
Date Stamp	10 May 2017 17:07:12			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-74\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	64	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.0605	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.000

CWW-I-74-13C.esp

VerticalScaleFactor = 1

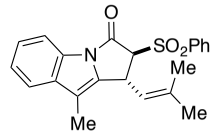


4-55
E:*Z* = 1:3.1

Acquisition Time (sec)	3.2768	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	10 May 2017 17:15:44
Date Stamp	10 May 2017 17:15:44			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-97A-T1\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	54.49	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.6931	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.997

CWW-I-97A-T1-1H.esp

VerticalScaleFactor = 1

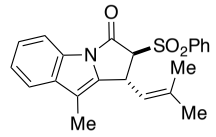


4-54

Acquisition Time (sec)	1.1010	***Comment***	5 mm CPPBBO BB-1H/19F/D Z-GRD Z122624/0039			***Date***	10 May 2017 17:17:52
Date Stamp	10 May 2017 17:17:52			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-97A-T1\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	32	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12572.5137	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.003

CWW-I-97A-T1-13C.esp

VerticalScaleFactor = 1

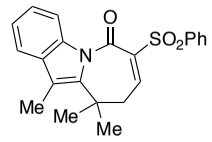


4-54

Acquisition Time (sec)	3.2768	***Comment***	5 mm PABBO BB/19F-1H/D Z-GRD Z113652/0157			***Date***	21 Aug 2015 13:06:08
Date Stamp	21 Aug 2015 13:06:08			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-97A-T2\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	62.07	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3072.7258	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.609

CWW-I-97A-T2-1H.esp

VerticalScaleFactor = 1



4-60

Acquisition Time (sec)	1.1010	***Comment***	5 mm PABBO BB/19F-1H/D Z-GRD Z113652/0157			***Date***	21 Aug 2015 13:10:24
Date Stamp	21 Aug 2015 13:10:24			***File Name***	\\Mac\Home\Documents\GA Tech Research\NMR Files\CWW-I-97A-T2\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	20	***Origin***	spect
Original Points Count	32768	***Owner***	cwilliam	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12566.6113	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.929

CWW-I-97A-T2-13C.esp

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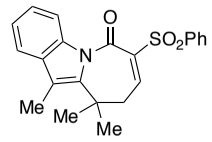

4-60

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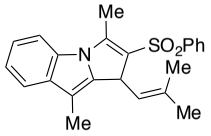

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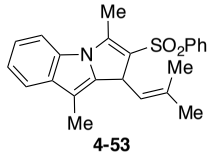

4-53

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CHAPTER 5. CONCLUSIONS AND FUTURE OUTLOOK

5.1 Novel Homo-Nazarov Cyclization Methodologies

Firstly, a number of novel variants of the homo-Nazarov cyclization were explored. Using DACPs, catalytic ring-opening reactions of cyclopropanes can be readily achieved under mild conditions. Moreover, the synthesis of cyclopropyl vinyl ketones is carried out in a modular route, allowing access to a variety of different starting materials. Because of the modular synthetic route and mild ring-opening conditions, a very broad substrate scope can be achieved and a breadth of chemical space is accessed. The first catalytic and chemodivergent interrupted homo-Nazarov cyclization using allylsilanes nucleophiles was developed, giving rapid access to densely functionalized α-allyl cyclohexenol and hexahydrobenzofuran products. The first catalytic, arylative, interrupted homo-Nazarov cyclization protocol was also investigated, providing a modular route to α-(hetero)aryl cyclohexenols. The first example of an intramolecular formal homo-Nazarov cyclization/Friedel-Crafts-type arylation was also demonstrated. Finally, the synthesis of the anticancer natural product propolisbenzofuran B was pursued utilizing a homo-Nazarov cyclization synthetic route.

The work contained within this dissertation revolving around the methodologies and application of DACPs will further inform the synthetic chemistry community of the utility of DACPs in the synthesis of densely functionalized carbocycles. Within the proposed route to propolisbenzofuran B, further evidence of the utility of DACPs toward synthesis of natural products will be provided.

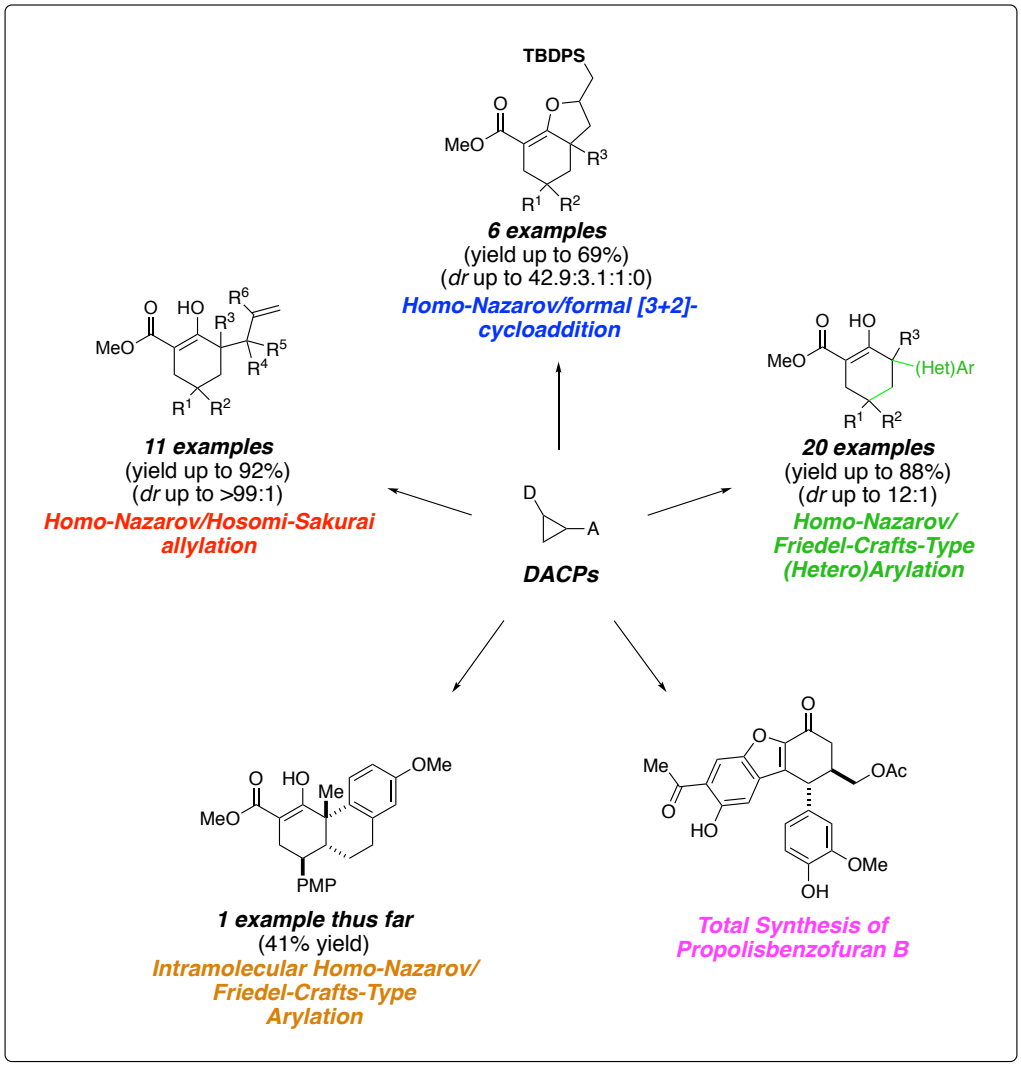
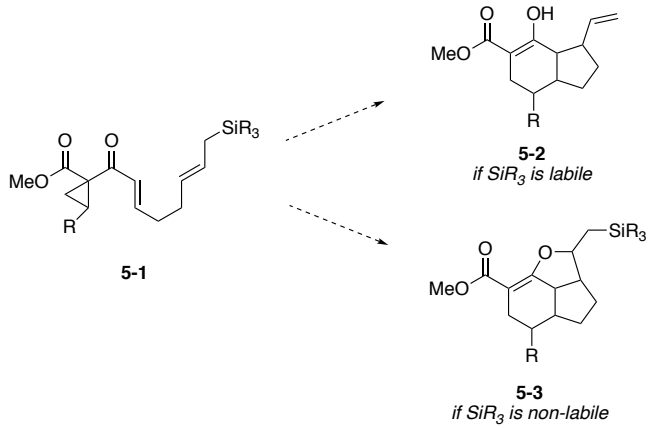


Figure 5.1 Utility of DACPs Investigated Within This Dissertation

5.2 Further Exploration of Interrupted Formal Homo-Nazarov Methodologies

Chapter 2 explored the using of DACPs in Lewis acid-catalyzed interrupted formal homo-Nazarov cyclizations using allylsilanes and (hetero)arenes toward the interception of cyclic oxyallyl cations. This methodological investigation resulted in the synthesis of densely functionalized α-allyl cyclohexenols, hexahydrobenzofurans, and α-(hetero)aryl cyclohexenols. In this chapter, the first example of an intramolecular variant

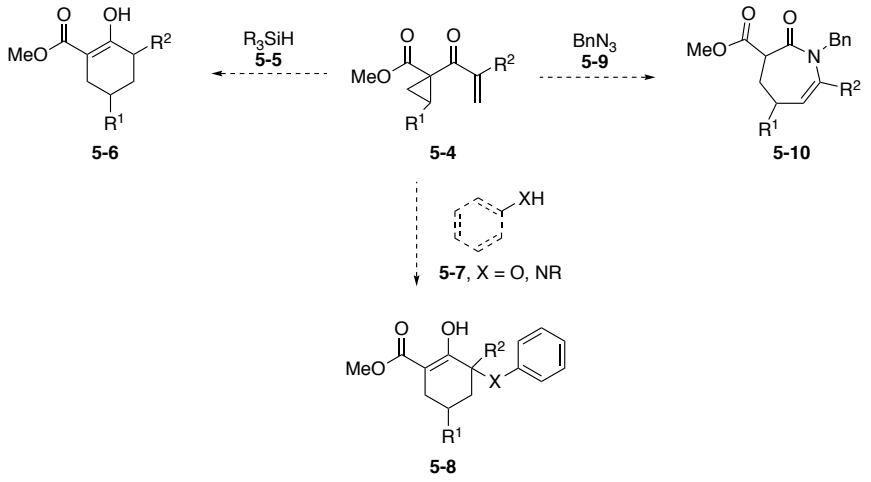
of the interrupted formal homo-Nazarov was also demonstrated. This proof-of-concept should provide a springboard for the development of an intramolecular, arylative, interrupted formal homo-Nazarov cyclizations of the same type. It should also provide inspiration toward other intramolecular variants of this methodology, including that with a tethered allylsilane nucleophile (Scheme 5.1). In this case, if a labile tethered allylsilane is used, one might envision the synthesis of vinyl-substituted hexahydroindanes of type **5-2**. In the case that a non-labile silyl nucleophile is used, the synthesis of oxatricylic compounds of type **5-3** could be readily achieved.



Scheme 5.1 Intramolecular Allylsilane-Interrupted Formal Homo-Nazarov Methodology

Beyond this potential methodological advance, a number of other interrupted formal homo-Nazarov methodologies with other nucleophiles could also be envisioned for the achievement of molecular complexity (Scheme 5.2). Using silane reducing agents, a reductive formal homo-Nazarov methodology might be achieved. Heteroatom nucleophiles could also be envisioned toward molecules of the type **5-8**. Finally, in an attempt to synthesize azepine core scaffolds of the type **5-10**, an azide nucleophile could be used, resulting in an azide trapping/Schmidt reaction cascade. These reactions could

further show the synthetic utility of interrupted formal homo-Nazarov cyclization reactions and provide access to broader chemical space.

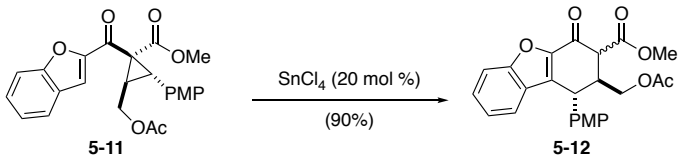


Scheme 5.2 Further Expansions of the Interrupted Formal Homo-Nazarov Methodology

5.3 Synthesis of Propolisbenzofuran B Analogs Via Formal Homo-Nazarov Cyclization Methodology

In Chapter 4, appreciable progress was made toward the synthesis of propolisbenzofuran B utilizing a formal homo-Nazarov cyclization (FHN) to form the benzofuran-fused cyclohexanone core (Scheme 5.3). This protocol has already been shown to have broad substrate scope. Because of this, we believe that this cyclization methodology will provide access to a number of unnatural (and more drug-like) analogs of propolisbenzofuran B. After completion of the synthesis of the target, we hope to synthesize a number of synthetic analogs of propolisbenzofuran B and launch an investigative study into the structure-activity relationships of other fused heteroaromatics, such as those shown in Figure 5.2. By using this methodology in the synthesis of

propolisbenzofuran B, we hope the synthetic community will realize the potential of cyclopropane ring-opening/ring-closing cyclizations.



Scheme 5.3 Synthesis of Benzofuran-Fused Cyclohexanone Core by FHN Cyclization

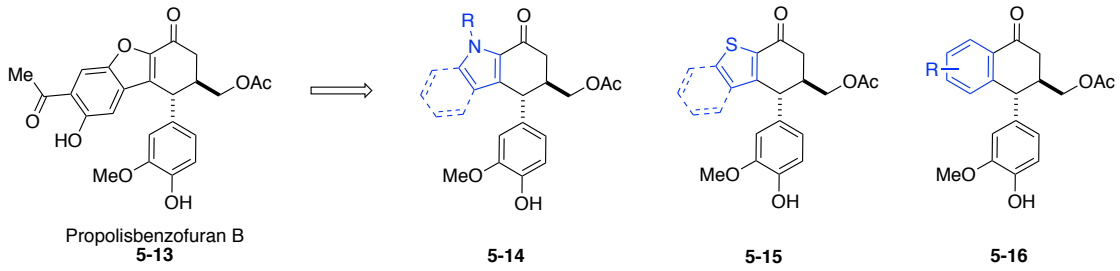
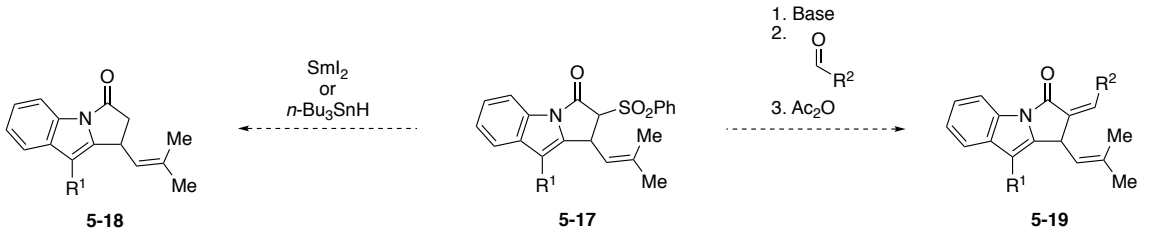


Figure 5.2 Unnatural Propolisbenzofuran B Synthetic Analogs

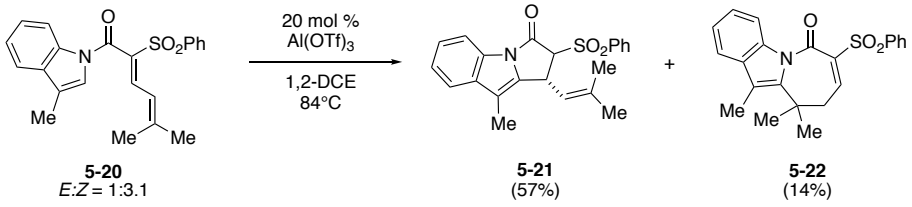
5.4 Development of a Vinyligous Aza-Nazarov-Like Friedel-Crafts-Type Cyclization Toward Indole-Fused Azepines

In Chapter 4, as part of the progress toward the synthesis of the flinderoles, a novel unsaturated α-sulfonylamide was used as the key precursor toward the pyrrolo[1,2-*a*]indole framework. To our knowledge, this is a novel precursor in Nazarov cyclizations. The sulfonyl groups allow for a whole range of reactivity after a Nazarov cyclization step, such as reductive desulfonylations and Julia olefinations. As such, access to synthetic analogs of the flinderoles could be rapidly achieved (Scheme 5.4). In the case of the Julia olefination to synthesize intermediates of type **5-19**, subsequent Michael-type addition reactions could be utilized to further derivatize the substrates.

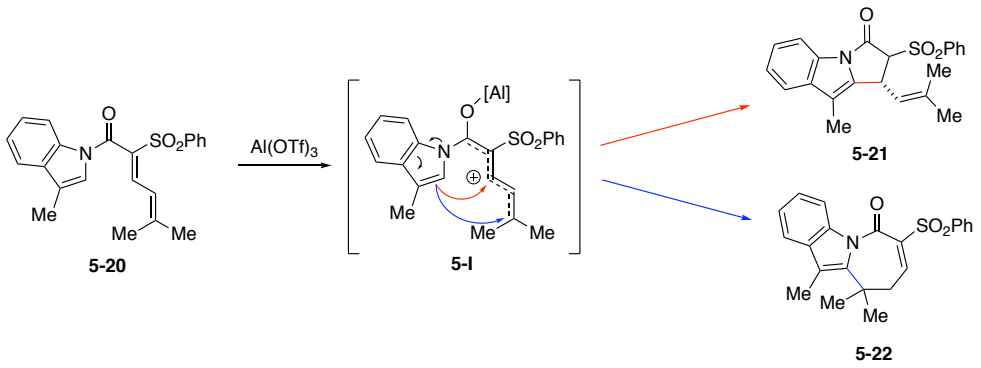


Scheme 5.4 Examples of Desulfonylation Reactions for Flinderole Derivatization

In the process of the aza-Nazarov-like Friedel-Crafts-type (ANFC) cyclization, an interesting side product was formed as part of the ANFC reaction step. In addition to the suspected (and desired) pyrrole **5-15**, the 7-membered azepine **5-16** was also isolated (Scheme 5.5). To our knowledge, this represents the first reactivity of this type. We hypothesize that this reactivity stems from the likelihood that this reaction does not proceed via a concerted mechanism, mimicking a more Friedel-Crafts-type process (hence the nomenclature, ANFC). In addition to the more Friedel-Crafts-type mechanism, it is also suspected that the increased electron-withdrawing nature of the sulfonyl group further added to the cationic character of the second vinyl group, leading to addition at the distal carbon (Scheme 5.6). While much optimization is needed, this proof-of-concept reaction should give other chemists inspiration to pursue this type of reactivity further. If this methodology is viable, it will provide yet another method to access azepinoindole scaffolds found in many natural products.



Scheme 5.5 Synthesis of Indole-Fused Azepines Via an ANFC Cyclization



Scheme 5.6 Suspected Mechanism for Formation of the Pyrrole and Azepine Products

5.5 Conclusion

Within this dissertation, a few novel methodological advances were pioneered in the realm of ANFC reactions and interrupted FHN cyclizations. As such, the synthetic community will have found new methods to access α-allylcyclohexenols, hexahydrobenzofurans, and α-(hetero)arylcyclohexenols. A FHN methodology was pursued to access the benzofuran-fused cyclohexanone core of the anticancer natural product propolisbenzofuran B. An ANFC cyclization methodology was investigated toward the synthesis of the antimalarial flindersial alkaloids. Additionally, as part of the ANFC protocol, a new method to access azepino[1,2-*a*]indoles was uncovered, though much optimization is still needed. In each of the developed methodologies and syntheses, modular synthetic routes toward synthetic precursors were targeted in order to further investigate and expand the substrate scope, pushing the boundaries of what these methodologies will tolerate. As such, these methodologies can now be applied in the synthesis of many bioactive natural products and other pharmaceutically relevant compounds by the synthetic community.

APPENDIX I. DEHYDRATIVE NAZAROV-TYPE ELECTRO-CYCLIZATIONS OF ALKENYL (HETERO)ARYL CARBINOLS VIA CALCIUM CATALYSIS[†]

I.1 Cyclopenta[*b*]thiophenes: Relevance

Cyclopenta[*b*]thiophenes represent a unique isostere of indene that often exists as an equilibrium mixture of 3 forms: a 4*H*- and 6*H*- isomers, and a 5*H*-isoindene isostere (Figure I.1).[1-3] The utility of cyclopenta[*b*]thiophenes is generally in the synthesis of metal complexes;[4-12] however, their dihydro- derivatives are often used in the materials science community[13-18] and in the realm of medicinal chemistry.[19-22] While only a few syntheses of these unique structures have been reported, most involve the elaboration of thiophene-fused cyclopentanones. However, most have limited substrate scope and low functional group tolerance. Therefore, there exists a need for a highly general method for the synthesis of these cores.

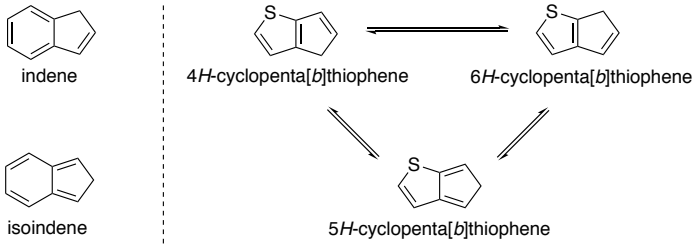
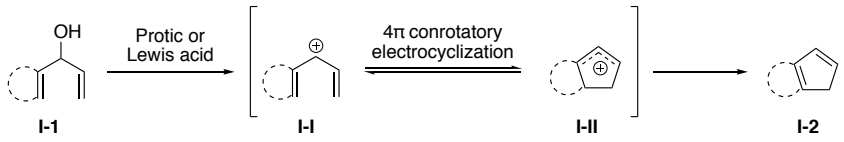


Figure I.1 Isomers of Cyclopenta[*b*]thiophenes

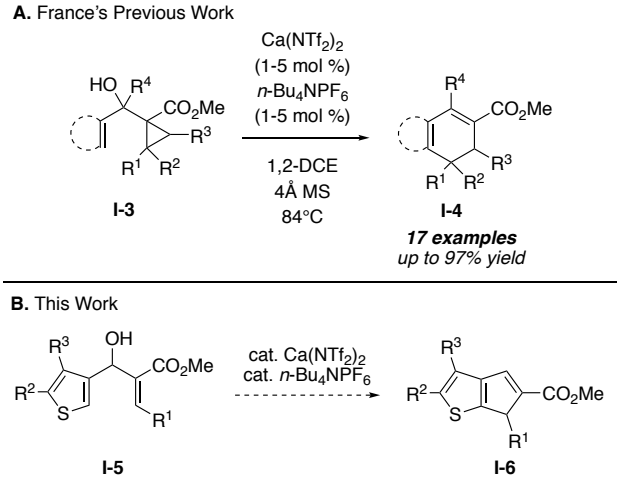
[†] This work was conducted in collaboration with M. Cynthia Martin, Matthew J. Sandridge, and Zola A. Francis. My contribution included the synthesis and extensive purification of many of the β-ketoester and (hetero)aryl allylic alcohol starting materials, the attempted Diels-Alder derivatizations and editing to the report. Published in *Tetrahedron*, **2017**, *73*, 4093-4108.

I.2 Nazarov-like Cyclizations Toward Cyclopenta[*b*]thiophenes

A recent re-emergence of interest in the Nazarov and Nazarov-like cyclizations has led to the development of many elegant methods toward the synthesis of highly functionalized cyclopentanes. In several such examples, ionization of the C-O bond of divinyl or heteroaryl-substituted allylic alcohols[23-34] leads to the formation of cyclopentadienes and (hetero)aryl-fused cyclopentadienes via a 4π-electrocyclization approach, often coined as a "dehydrative Nazarov" or "cyclodehydration" (Scheme I.1).[35-37] Recently, the France group recently reported a calcium-catalyzed, dehydrative ring-opening cyclization of (hetero)aryl cyclopropyl carbinols for the formation of (hetero)aryl-fused cyclohexa-1,3-dienes (Scheme I.2A).[38] Inspired by these results, we sought to develop a similar catalytic, generalizable approach toward the synthesis of cyclopenta[*b*]thiophenes, which have been particularly synthetically challenging substrates when utilizing a dehydrative Nazarov-like approach (Scheme I.2B).[39-40]



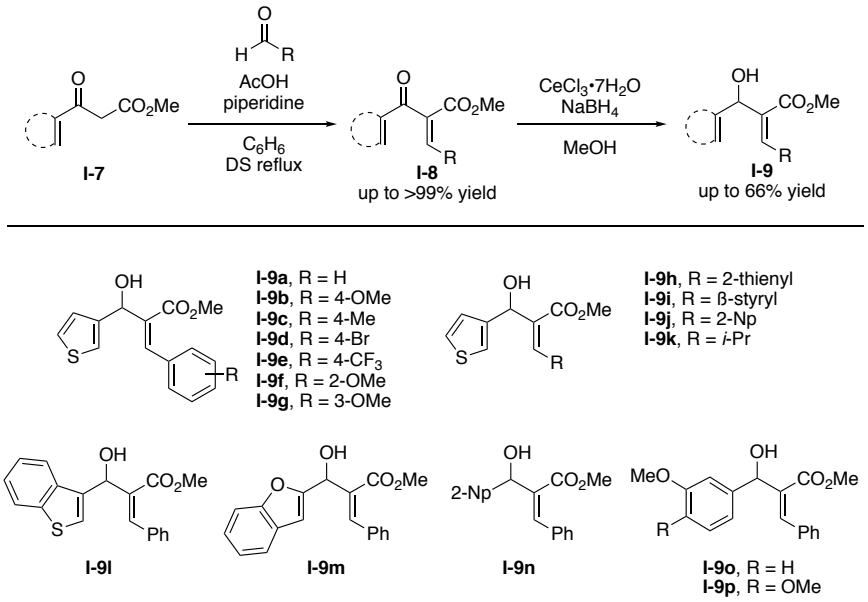
Scheme I.1 Mechanism of the Dehydrative Nazarov Cyclization



Scheme I.2 Calcium-Catalyzed, Dehydrative Cyclization Strategies

I.2.1 Synthesis of (Hetero)aryl Allyl Carbinols

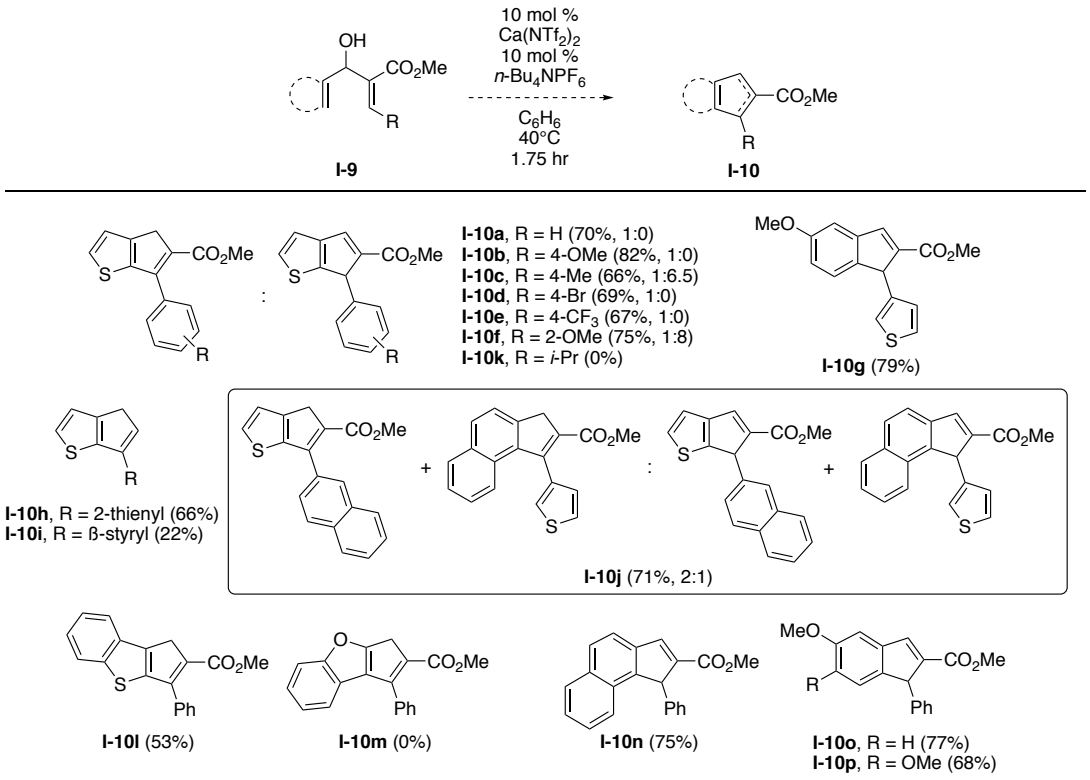
Guided by Batey's previous investigation of substituent effects in the dehydrative Nazarov cyclization toward functionalized indenes,[41] we laid out a rather simple 2-step approach toward the desired (hetero)aryl allyl carbinol starting materials from known ß-ketoesters (Scheme I.3). In the first step, a Knoevenagel condensation of ß-ketoesters **I-7** with chosen aldehydes yielded the desired unsaturated ß-ketoesters **I-8** in up to quantitative yield. Following this, Luche reductions to form the subsequent carbinols **I-9** occurred in up to 66% yield. However, these substrates often required multiple, careful chromatographic purifications.



Scheme I.3 Synthesis of (Hetero)Aryl Allyl Carbinols

I.2.2 Reaction Optimization and Substrate Scope

Upon synthesis of substrate **I-9a**, an extensive set of reaction optimization screens were carried out, including those examining Lewis/Brönsted acid catalysts, catalyst loadings, temperatures, solvents, concentration, and reaction time, which will not be discussed in detail here. It was determined that the optimized conditions were 10 mol % $Ca(NTf_2)_2$, 10 mol % *n*-Bu_4NPF_6 in benzene (0.05 M) at 40°C for 1.75 hours. With this set of conditions in hand, the substrate scope of the reaction was examined (Scheme I.4).



Scheme I.4 Examination of Substrate Scope

In order to examine the electronic effects of differing substituents about the phenyl ring, carbinols **I-9a-e** were subjected to the optimized conditions. When a strong electron-donating group such as 4-methoxy is added to the ring, yield increases to 82%. However, when an electron-withdrawing group such as 4-trifluoromethyl is added, yield slightly decreases to 67%. This suggests only a small inductive effect on the outcome of the reaction, where yields are increased with electron-donating nature and slightly decreased with electron-withdrawing nature of the substituents.

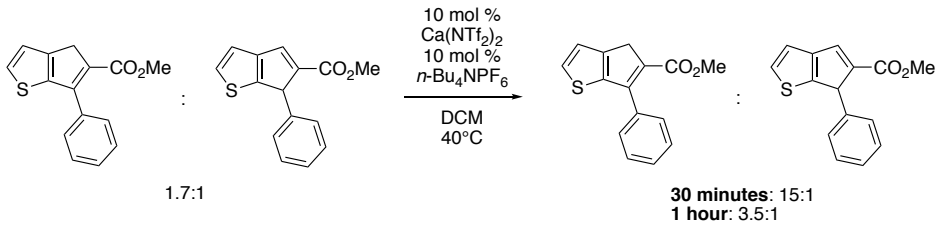
When a 2-methoxy group is added (**I-9f**), the reaction favors the 6*H*-cyclopenta[*b*]thiophene, likely due to a steric effect slowing the rate of alkene isomerization to the more thermodynamically preferred 4*H*-cyclopenta[*b*]thiophene. However, when a 3-methoxy substituent (**I-9g**) is employed, the reaction is completely selective for the indene product due to the increased nucleophilicity of the position *para*

to the methoxy group over the 2-position of the thiophene. In the case of the 2-thienyl moiety **I-9h**, no attack is observed at the 3-position of the thiophene, suggesting the 2-position of the thiophene is more nucleophilic than the 2-position. In an extended π-system (**I-9i**), only 22% yield is observed. This is likely due the generation of competing cationic intermediates, leading to multiple side products.

When a 2-naphthyl substituent is used, four different products are observed as an only slightly determinable mixture of isomers. Only the ratio of the combined tetrasubstituted and trisubstituted alkene isomers was determinable. In the case that a purely alkyl substituent is used (**I-9k**), only an indeterminable mixture of products is observed, although a mixture of **I-9k** and its fully reduced alkyl alcohol was used. Other (hetero)arenes in place of the 3-thienyl moiety were also examined (**I-9l-p**), with good tolerance for most substrates. However, when the 3-thienyl is replaced with a 2-benzofuran, only decomposition of the starting material is observed.

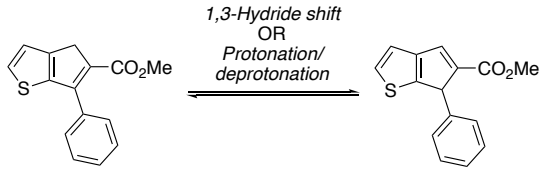
I.2.3 Probing Interconversion of the 4H- and 6H-Cyclopenta[b]thiophenes

During the course of the study, it was observed that the 4*H*- and 6*H*-cyclopenta[*b*]thiophene products obtained from this methodology often interconverted over the course of the reaction when ran in dichloromethane as solvent. In order to gain a deeper understanding of this phenomenon, a 1.7:1 mixture of the tetra- and trisubstituted alkene products **I-10a** were subjected to the optimized catalyst and concentration reaction conditions and monitored over time. A significant increase in the amount of the tetrasubstituted product was observed after only 30 minutes in refluxing dichloromethane (15:1); however, if left stirring at reflux for 1 hour, the selectivity eroded significantly to 3:5:1 (Scheme I.5).



Scheme I.5 Probing Isomerization of Products over Time

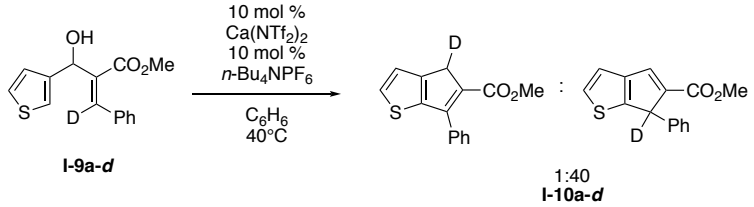
Two plausible mechanisms exist for the isomerization of the two products: one involves a 1,5-hydride shift, while the other is simple a protonation/deprotonation pathway (Scheme I.6). There also exists the possibility of some continuum between the two. A series of reactions were conducted to probe the viability of each of these mechanisms. When the products **I-10a** are exposed to a Brönsted acid ($HNTf_2$) in benzene at 40°C, only little erosion of selectivity toward the tetrasubstituted alkene is observed, suggesting the observed isomerization is likely only very slightly driven by a protonation/deprotonation mechanism. However, when exposed to the Lewis acid, significant, oscillating isomerization occurs over time. This leads to speculation that a complex involving the calcium catalyst and the products may promote interconversion.



Scheme I.6 Plausible Mechanisms for Interconversion

In order to determine the likelihood of the 1,5-hydride shift mechanism, a simple deuterium labeling study to probe any kinetic isotope effects was conducted by placing a deuterium atom at the α-position to the phenyl ring (Scheme I.7). Interestingly, when this deuterated **I-9a** starting material was subjected to the optimized reaction conditions for 30 minutes, 60 minutes, and 105 minutes, a 1:40 ratio of the tetrasubstituted to the

trisubstituted alkene products were obtained in all three circumstances, suggesting a large kinetic isotope effect on the 1,5-hydride shift.

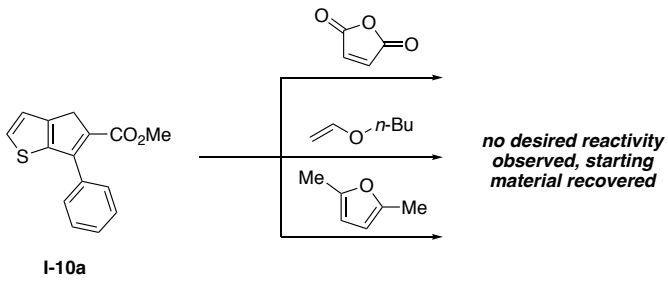


Scheme I.7 Deuterium Labeling Studies to Probe Kinetic Isotope Effects

Throughout these investigations, we were lead to several conclusions regarding the isomerization mechanism. Firstly, the trisubstituted product is formed first in the reaction mixture, and any tetrasubstituted alkene isomer is the result of an isomerization. Secondly, there exists a large kinetic isotope effect for isomerization. Thirdly, the calcium catalyst is not required for isomerization, although it does promote significant isomerization quickly. Although not discussed here, a solvent effect is also observed on the rate of isomerization of the tetra- and trisubstituted alkene products. Finally, some product degradation was observed over the course of the study, although it can be ruled as irrelevant in context of the observed erosion of isomer selectivity over reaction time.

I.2.4 Attempted Derivatization of Cyclopenta[b]thiophene Products

While Skramstad reported that 5*H*-cyclopenta[*b*]thiophenes were able to undergo Diels-Alder-type cyclizations, we set out to probe the viability of these reactions on the observed 4*H*-cyclopenta[*b*]thiophenes (Scheme I.8). However, when exposed to maleic anhydride (as a probe for normal electron demand cycloaddition), *n*-butyl vinyl ether (to probe for inverse electron demand cycloaddition), or 2,5-dimethylfuran (to probe the cyclopenta[*b*]thiophene as a dienophile), no desired reactivity was observed under any circumstances. Instead, only starting material was recovered.



Scheme I.8 Attempted Derivatizations

I.3 Conclusion

In summary, a calcium-catalyzed method for the synthesis of cyclopenta[*b*]thiophenes via a dehydrative Nazarov-like cyclization of (hetero)aryl alkenyl alcohols was disclosed. As such, it is one of the only known catalytic dehydrative Nazarov cyclization protocols in which thiophene rings are tolerated. Starting materials are accessed via a simple two-step route from known β-ketoesters, and products are obtained in up to 82% yield. A number of substituents were tolerated in this protocol, including aryl and heteroarenes substituents on the alkene. Cyclization generally occurs on the most nucleophilic ring, although mixtures are observed when nucleophilicities are similar. The arene series generally favors the trisubstituted alkene isomer, whereas the 2-thienyl series favors the tetrasubstituted isomer. In the future, we hope to further improve the synthesis of the starting materials (particularly the Luche reduction), expand the scope of the reaction, and potentially utilize these molecules in the development of organometallic catalysts.

I.4 Experimental Section

For all experimental data, including detailed experimental procedures, optimization tables, characterization data, and spectra, see Sandridge, M. J.; Martin, M.

C.; Williams, C. W.; Francis, Z. A.; France, S. "Dehydrative Nazarov-type electrocyclizations of alkenyl (hetero)aryl carbinols via calcium catalysis: Access to cyclopenta[*b*]thiophenes and indene derivatives." *Tetrahedron*, **2017**, *73*, 4093-4108.

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APPENDIX II. α-ALKYLIDENE-γ-BUTYROLACTONE FORMATION VIA BI(OTF)$_3$-CATALYZED, DEHYDRATIVE, RING-OPENING CYCLIZATIONS OF CYCLOPROPYL CARBINOLS[§]

II.1 α-Alkylidene-γ-butyrolactone (ABL) Framework: Relevance

The α-alkylidene-γ-butyrolactone (ABL) framework is found in a number of bioactive natural products, making it a relevant core both to the medicinal and synthetic organic chemistry community (Figure II.1).[1-4] By 2009, it was estimated that over 5000 ABL natural products and over 9000 synthetic analogs had been identified.[5] Historically, ABLs have also been rather simple to derivatize, with hydrogenations,[6] epoxidations,[7] conjugate additions,[8] and amine additions[9] being reported. ABLs are generally synthesized in a variety of ways: installation of alkylidenes on γ-butyrolactones,[10-13] lactonization,[14-19] one-pot C-H insertion/olefination,[20-22] cross metathesis,[23-24] Dreiding-Schmidt organometallic approach,[25] Pd-catalyzed cross-coupling,[26] enyne metathesis,[27] (retro-)Diels-Alder approaches,[28-29] radical cyclizations,[30-31] and Baeyer-Villiger approaches.[32] Considering the synthetic importance of these ABL molecules, and despite the wealth of methodologies to currently access them, the continuation of methodological development to access these scaffolds is a meaningful endeavor.

[§] This work was conducted in collaboration with Matthew J. Sandridge and Brett D. McLarney. My contribution to this project involved the synthesis of several cyclopropyl carbinol starting materials, purifications, cyclizations, and editing to the report. Published in *J. Org. Chem.* **2017**, *82*, 10883-10897.

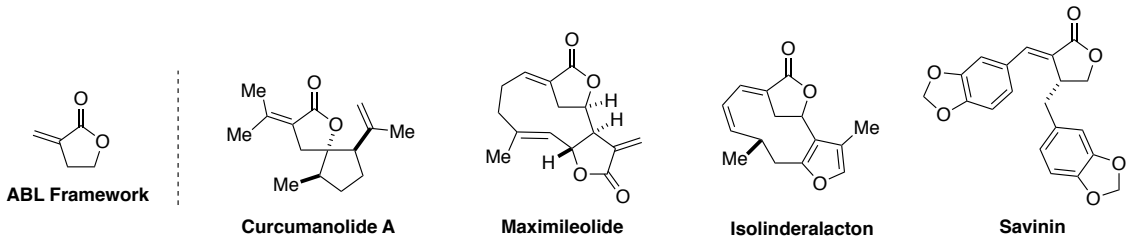
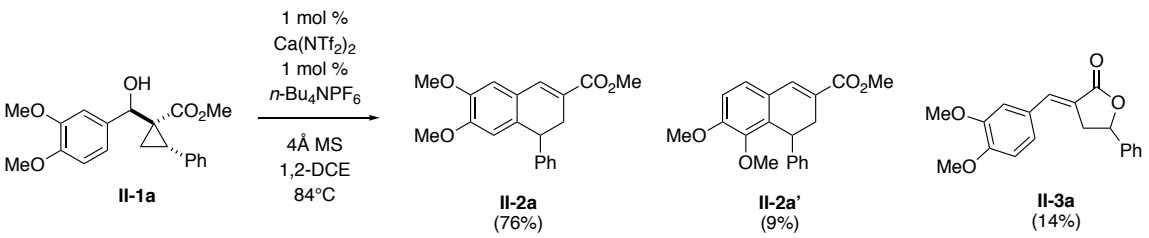


Figure II.1 ABL Scaffolds in Bioactive Molecules

II.2 Ring-opening Cyclizations: A New Approach to ABLs

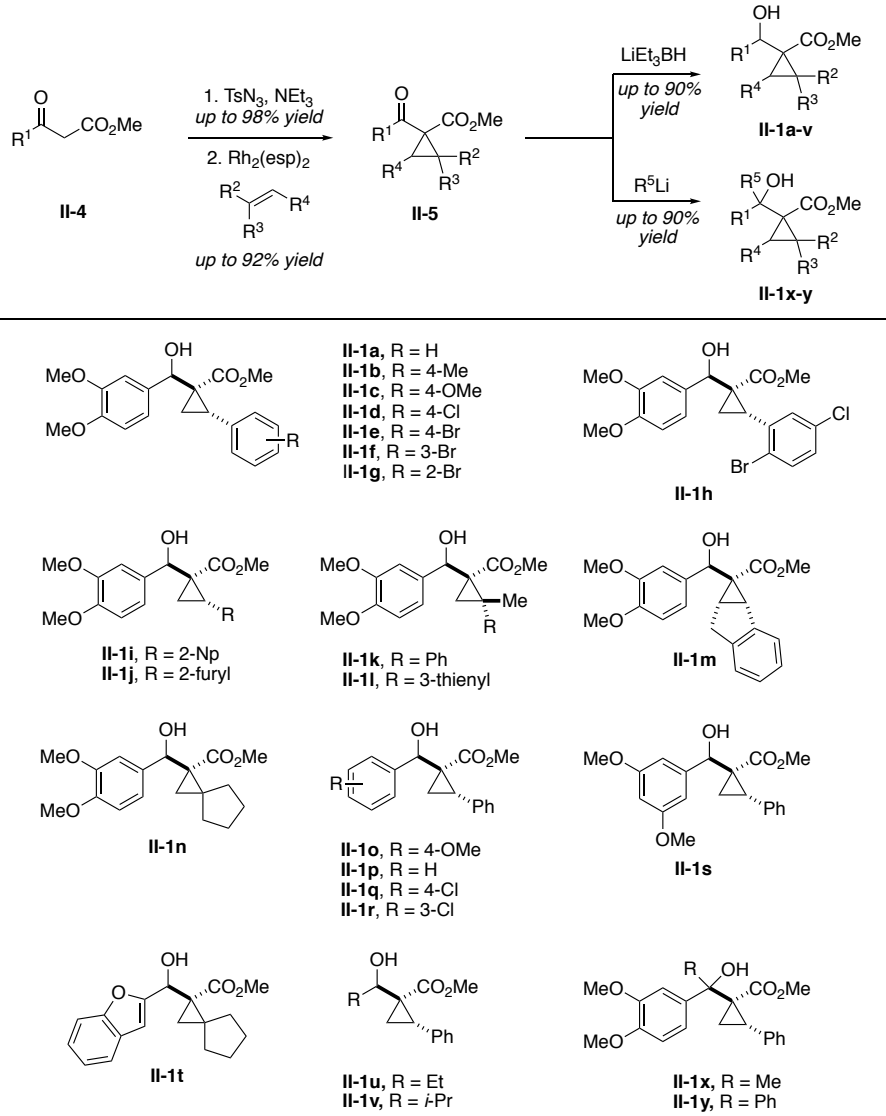
In 2017, the France group published a calcium-catalyzed, ring-opening cyclization approach to (hetero)aryl-fused cyclohexa-1,3-dienes utilizing (hetero)aryl cyclopropyl carbinols (Scheme II.1). Over the course of that study, it was discovered that when the model substrate was subjected to the optimized reaction conditions, a unique ABL product (**II-3a**) was also isolated in 14% yield.[33] In all other similar transformations, there was no mention of this unique product being formed.[34-35] While vinyl cyclopropanes have been used to form ABLs in the past with substituted benzaldehydes in the presence of DABCO,[36] there were no reports utilizing cyclopropyl carbinols. Fascinated by this result, we began an investigation to determine necessary conditions for selective ABL formation, with the goal of probing the factors that control chemoselectivity (ABL vs. dihydronaphthalene products) including the role of substituent effects.



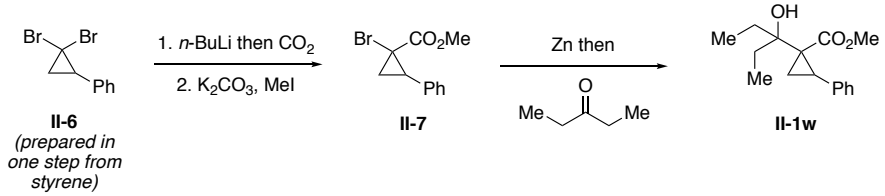
Scheme II.1 France's Previous Investigation of Ring-Opening Cyclization of Cyclopropyl Carbinols

II.2.1 Synthesis of Cyclopropyl Carbinols

Most cyclopropyl carbinols were synthesized via the same three-step route previously used by France and co-workers (Scheme II.2).[33] From the known β-ketoesters **II-4** the cyclopropanes were synthesized via diazo transfer followed by a Rh-catalyzed cyclopropanation. To generate secondary cyclopropyl carbinols (**II-1a-v**), $LiEt_3BH$ was used to reduce the corresponding ketone. Tertiary alcohols (**II-1x-y**), however, were generated via organolithium attack on the cyclopropyl ketones. In one unique case (**II-1w**), Nishii's Reformatsky approach was used (Scheme II.3).[37]



Scheme II.2 Synthesis of Cyclopropyl Carbinols



Scheme II.3 Reformatsky Approach to **II-1w**

II.2.2 Optimization and Investigation of Substrate Scope

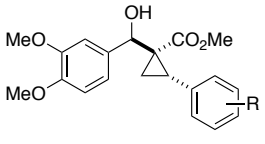
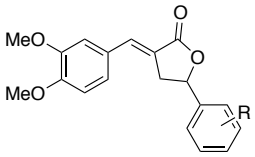
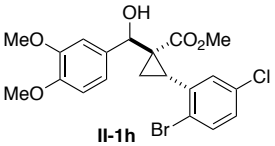
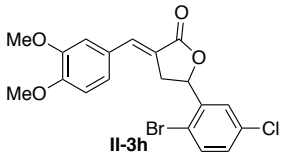
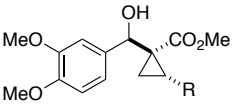
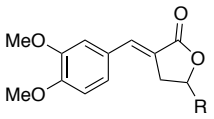
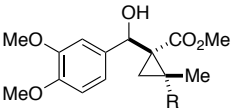
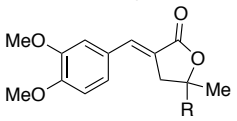
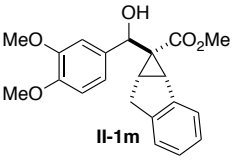
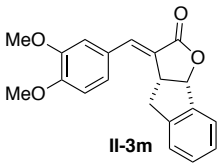
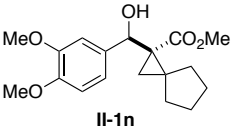
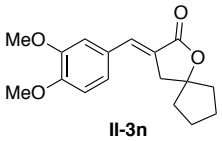
Upon obtaining substrate **II-1a**, an extensive set of optimization screens was carried out, including Lewis/Brönsted acid catalysts, catalyst loading, solvent, temperature, and concentration screens. Although they will not be discussed further here, the optimized conditions for ABL formation from **II-1a** were determined to be 5 mol % $Bi(OTf)_3$ in DCM (0.1 M) with 4Å molecular sieves at room temperature, giving the desired ABL in 62% yield. Over the course of the optimization, it was hypothesized that $Bi(OTf)_3$ was serving as a surrogate to the in situ generation of TfOH. After a series of control reactions including those with protic acids (including 15 mol % TfOH, which performed similarly to $Bi(OTf)_3$ with 61% yield), the addition of base, and probing other Bi(III) salts, it was determined that $Bi(OTf)_3$ indeed serves as an easy-to-handle precursor to TfOH. It is also worth noting that an equivalent of water is required for ABL formation; higher equivalencies of water are detrimental to the cleanliness of the reaction, which the molecular sieves help to control.

Upon obtaining optimized conditions, substrate scope for the reaction was examined. Firstly, the effects of the cyclopropane substituent were investigated (Table II.1). It was quickly recognizable that electron-rich donors on the cyclopropane group greatly favored the formation of the dihydronaphthalene products (for instance, **II-1c)**, while less electron-rich donors typically favored ABL formation (**II-1a, b**, **d-h**). Yield generally increases with greater electron deficiency, and most are isolated as a single diastereomer. A 2-naphthyl donor is tolerated, giving **II-3i** in 24% yield as a single diastereomer. However, a 2-furyl donor (**II-1j**) gives only an intractable mixture. For the α-methyl phenyl cyclopropyl carbinol **II-1k**, the desired ABL is obtained in 38% yield as

a single diastereomer. In the disubstituted cyclopropyl carbinols **II-1l-n**, an elimination product was also observed (Figure II.2). However, indanyl and spirocyclopentyl ABLs **II-3m** and **II-3n** were obtained in 34% and 43% yields and 5:1 and 1:1 *E:Z* ratios, respectively.

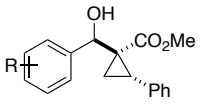
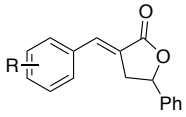
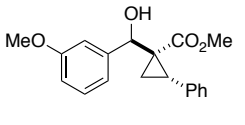
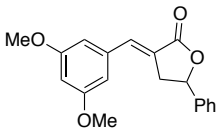
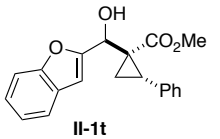
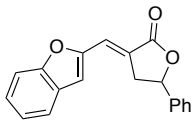
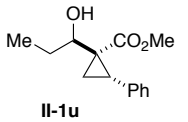
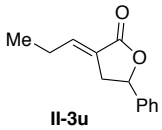
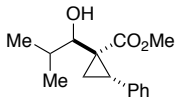
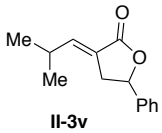
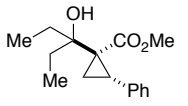
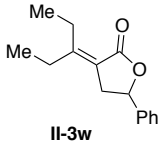
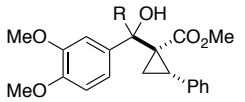
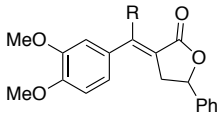
When the effects of the (hetero)aryl substituent were examined, it also became quite clear that the electronics of the system have a drastic effect on both the yield and *E/Z* ratio of products obtained (Table II.2). For instance, when the 3,4-dimethoxyphenyl group is replaced by a simple 4-methoxyphenyl group, yield increases to 73%; however, *E/Z* selectivity erodes to 7:1 (Table II.2, Entry 1). A simple phenyl, on the other hand, further decreases E/Z selectivity to 1:1 (Table II.2, Entry 2). When an electron-deficient arene is used (**II-1q-r**), yield decreases significantly, giving on 26% yield of the desired ABL **II-3q** as a 1:1 *E:Z* mixture or an intractable mixture, respectively. A benzofuran was tolerated, giving 48% of the desired ABL as a single diastereomer. Dialkyl carbinols (**II-1u-v**) were not effective substrates unless a tertiary alcohol (**II-1w**) was used. Tertiary benzylic carbinols were effective substrates, giving **II-3x** in 54% yield as a single diastereomer and **II-3y** in 41% yield as a 3:1 mixture of unassigned diastereomers.

Table II.1 Examination of Cyclopropane Donors

Entry[a]	Carbinol **II-1**	ABL **II-3**	Yield (%)[b]	*E:Z*[c]
				
1[d]	**II-1a,** R = H	**II-3a**	62	>99:1
2[d]	**II-1b**, R = 4-Me	**II-3b**	23	3:1[e]
3	**II-1c**, R = 4-OMe	**II-3c**	—[f]	—
4	**II-1d**, R = 4-Cl	**II-3d**	81	>99:1
5	**II-1e**, R = 4-Br	**II-3e**	87	>99:1
6	**II-1f**, R = 3-Br	**II-3f**	89	>99:1
7	**II-1g**, R = 2-Br	**II-3g**	72	>99:1
8[g]	 **II-1h**	 **II-3h**	78	>99:1
				
9	**II-1i**, R = 2-Np	**II-3i**	24	>99:1
10	**II-1j**, R = 2-furyl	**II-3j**	—[h]	—
				
11	**II-1k**, R = Ph	**II-3k**	38	>99:1
12	**II-1l**, R = 3-thienyl	**II-3l**	—[i]	—
13	 **II-1m**	 **II-3m**	34	—[j]
14	 **II-1n**	 **II-3n**	43[k]	1:1

[a]Reactions performed with 1 equiv. of cyclopropyl carbinol and 10 mol % $Bi(OTf)_3$ in DCM (0.1 M) at room temperature with 4Å molecular sieves. [b]Isolated yield after column chromatography. [c]*E/Z* ratios determined by crude NMR on crude mixtures. [d]5 mol % $Bi(OTf)_3$ used. [e]*E/Z* ratios determined by isolated yield of **(E)-II-3b** and ^{1}H NMR yield of **(Z)-II-3b** with dimethyl terephthalate as an internal standard. [f]Only the dihydronaphthalene product observed. [g]20 mol % $Bi(OTf)_3$ used. [h]Intractable mixture obtained. [i]No ABL products observed. [j]5:1 mixture of unassigned diastereomers. [k]12:1 mixture of dihydronaphthalene product and elimination product. ^{1}H NMR yield using dimethyl terephthalate as an internal standard.

Table II.2 Examination of (Hetero)aryl Carbinol Substituents

Entry[a]	Carbinol **II-1**	ABL **II-3**	Yield (%)[b]	*E:Z*[c]
				
1	**II-1o,** R = 4-OMe	**II-3o**	73	7:1[d]
2	**II-1p**, R = H	**II-3p**	60	1:1
3	**II-1q**, R = 4-Cl	**II-3q**	35[e]	1:1
4	**II-1r**, R = 3-Cl	**II-3r**	—[f]	—
5	 **II-1s**	 **II-3s**	26[e]	1:1
6	 **II-1t**	 **II-3t**	48	>99:1
7	 **II-1u**	 **II-3u**	—[g]	—
8	 **II-1v**	 **II-3v**	—[g]	—
9	 **II-1w**	 **II-3w**	27[e]	—
				
10[h]	**II-1x**, R = Me	**II-3x**	54	>99:1
11	**II-1y**, R = Ph	**II-3y**	41	—[i]

[a]Reactions performed with 1 equiv. of cyclopropyl carbinol and 10 mol % $Bi(OTf)_3$ in DCM (0.1 M) at room temperature with 4Å molecular sieves. [b]Isolated yield after column chromatography. [c]*E/Z* ratios determined by crude NMR on crude mixtures. [d]*E/Z* ratios determined by isolated yield of **(E)-II-3o** and **(Z)-II-3o**. [e]^{1}H NMR yield using dimethyl terephthalate as an internal standard. [f]Intractable mixture obtained. [g]No reaction; only starting material recovered. [h]5 mol % of $Bi(OTf)_3$ used. [i]3:1 mixture of unassigned diastereomers.

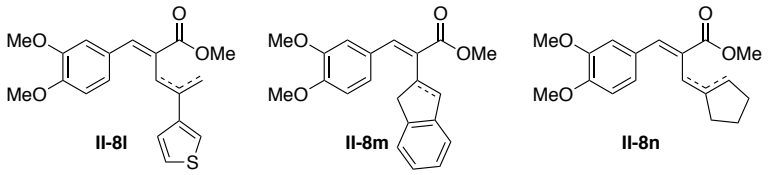


Figure II.2 Elimination Products

II.2.3 Rationalizing E/Z Selectivities Observed in ABL Products

With the substrate scope fully examined at this stage, it seemed prudent to investigate the origins of the observed *E/Z* selectivities. To summarize a series of computational calculations of the reaction coordinates of substrates **II-1a** and **II-1p**, as the electron-donating ability of the (hetero)aryl substituent of the carbinol decreases (e.g., 3,4-dimethoxyphenyl to phenyl), the molecule compensates by shifting atomic partial charge from C_α to C_γ, resulting in a slightly stronger, shorter, C_β-C_γ bond. The electron-donating potential of the cyclopropyl donor is also a factor in controlling *E/Z* selectivity. In the case of substrates **II-1a** and **II-1b**, as the electron-donating ability of the phenyl ring increases (R = H vs. R = Me), the C_β-C_γ bond is more polarized, and thus longer. As the C_β-C_γ bond lengthens, the energy gap between the *E* and *Z* isomer transition states decreases, leading to lower *E/Z* selectivities (Figure II.3).

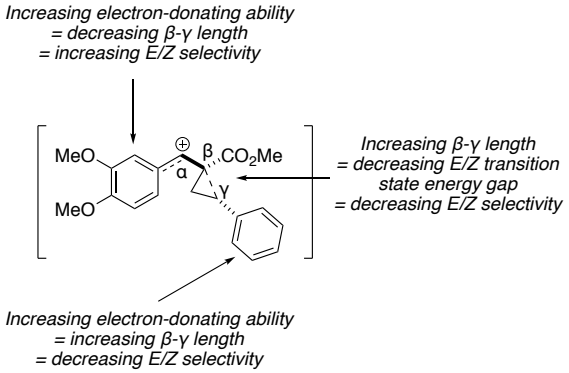


Figure II.3 Rationalization of *E/Z* Selectivity in ABL Products

II.3 Conclusion

In summary, a $Bi(OTf)_3$-catalyzed, dehydrative, ring-opening cyclization of (hetero)aryl cyclopropyl carbinols toward the synthesis of ABL frameworks has been developed. This represents a chemodivergent strategy from France's previous Lewis acid-catalyzed protocol toward the synthesis of functionalized dihydronaphthalene using the same (hetero)aryl cyclopropyl carbinol precursors. It was determined that $Bi(OTf)_3$ likely serves as an easy-to-handle surrogate to TfOH, which catalyzes the reaction and gives ABL products in up to 89% yield and up to >99:1 *E/Z* selectivity. The electron-donating ability of cyclopropane donors has a drastic effect on the chemoselectivity of the reaction, with more electron-deficient donors favoring ABLs over dihydronaphthalenes. Also as a part of this study, a comprehensive predictive model for E/Z selectivity was developed using computational methods. Using these methods, it was determined that the electronics of the (hetero)aryl substituent and the cyclopropyl donor group can greatly influence the cyclopropyl carbinyl cation C_β-C_γ bond length which correlated with the overall *E/Z* selectivity of the reactions. Future efforts will focus on the synthesis of ABL natural products utilizing this newly developed ring-opening strategy.

II.4 Experimental Section

For all experimental data, including detailed experimental procedures, optimization tables, characterization data, and spectra, see Sandridge, M. J.; McLarney, B. D.; Williams, C. W.; France, S. "α-Alkylidene-γ-butyrolactone Formation via $Bi(OTf)_3$-Catalyzed, Dehydrative, Ring-Opening Cyclizations of Cyclopropyl Carbinols:

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